Ph.D. Thesis

"SYNTHESIS AND PHYSICOCHEMICAL STUDIES OF SOME MOLECULES OF MEDICINAL INTEREST"

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(DST-FIST FUNDED & UGC-SAP SPONSORED)

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"SYNTHESIS AND PHYSICOCHEMICAL STUDIES OF SOME MOLECULES OF MEDICINAL INTEREST"

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IN

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BY

RAVI V. GAJERA

UNDER THE GUIDANCE

OF

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Saurashtra University

Rajkot- 360 005

Gujarat - (INDIA)

2010

Dedicated To My
Parents &
Beloved Guide

ACKNOWLEDGEMENT

First and foremost, I wish to pay my homage and devote my emotions to "LORD GAYATRI MAA", "The Wonderful Chemist" of this lovely world without whose blessings this task would not have been accomplished. I bow my head in utter humility and complete dedication.

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Synopsis

SYNOPSIS

"SYNTHESIS AND PHYSICOCHEMICAL STUDIES OF SOME MOLECULES OF MEDICINAL INTEREST"

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Synopsis of the Thesis submitted to the Saurashtra University for the degree of Doctor of Philosophy in Chemistry

Faculty	**:**	**Science**
Subject	**:**	**Chemistry**
Title	**:**	**Synthesis and physicochemical studies of some molecules of medicinal interest**
Name of the Candidate	**:**	**Ravi V. Gajera**
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SYNTHESIS AND PHYSICOCHEMICAL STUDIES OF SOME MOLECULES OF MEDICINAL INTEREST.

Medicinal or pharmaceutical chemistry is a scientific discipline at the intersection of chemistry and pharmacy involved with designing, synthesizing and developing pharmaceutical drugs. It deals with identification, synthesis and development of new chemical entities suitable for therapeutic use. In recent years, many researchers have been work on medicinal chemistry which involves various aromatic compounds including heterocyclic ring systems. Heterocyclic compounds are biologically active and they have a large number of applications in medicine and pharmacy.

Taking in view of the applicability of heterocyclic organic compounds, the present work was undertaken to synthesize some new heterocycles bearing pyrimidines and thiazole nucleus.

The work to be presented in the thesis entitled "Synthesis and Physicochemical studies of some molecules of medicinal interest" in divided into four Chapters.

Chapter-1 General Introduction

Chapter-2 Synthesis and characterization

Part-1 Synthesis of Pyrimidine Derivatives

Section-I Synthesis of Dihydropyrimidinones

Section-II Synthesis of Dihydropyrimidinethiones

Section-III Synthesis of N-methyl Dihydropyrimidinones

Section-IV Synthesis of Trtrahydropyrimidines

Part-2 Synthesis of Thiazole Derivatives

Synthesis of Azomethines

Chapter-3 Physicochemical properties

Section-I Acoustical Properties

Section-II Density and Refractive index

Section-III Conductance

Section-IV Solubility

Section-V Thermal Properties

Section-VI Dissociation Constants

Chapter-4 Biological activities

CHAPTER 1: General Introduction

This chapter describes literature survey of heterocyclic organic compounds, specially Pyrimidines and Thiazole derivatives. The synthesis, characterization, applications, physicochemical properties and antibacterial activities of pyrimidines and thiazole derivatives have also been discussed.

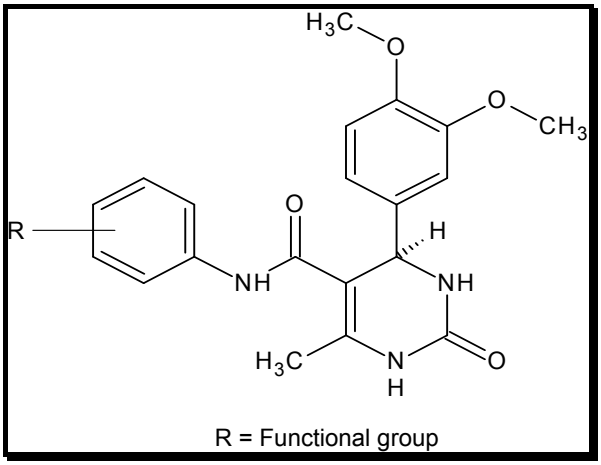
CHAPTER 2: Synthesis and Characterization

In this chapter, synthesis and characterization of various compounds are reported. It consists of two parts:

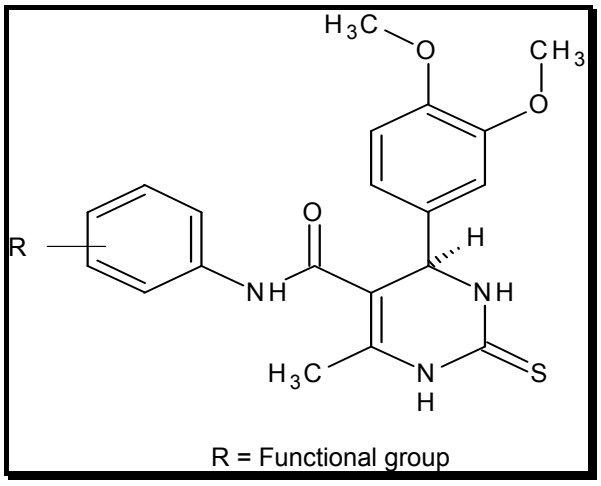
Part 1: Synthesis of Pyrimidine Derivatives

Four different types of pyrimidine Derivatives were synthesized which are given in four different sections.

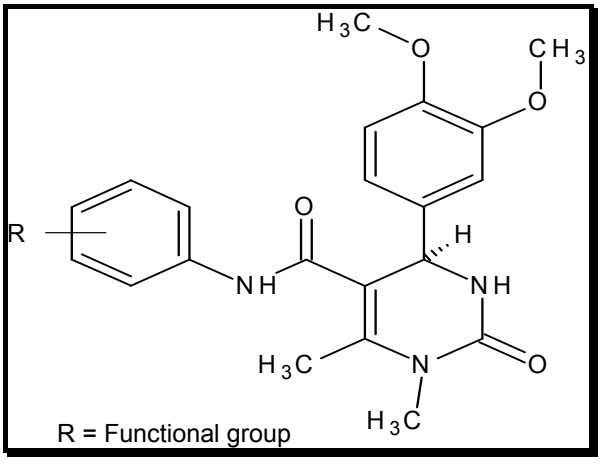
Section 1: Synthesis of Dihydropyrimidinones



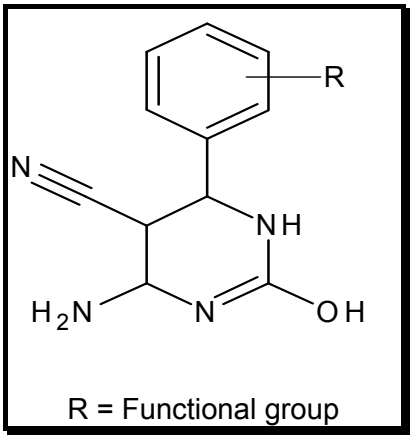
Section 2: Synthesis of Dihydropyrimidinethiones



Section 3: Synthesis of N-methyl Dihydropyrimidinones

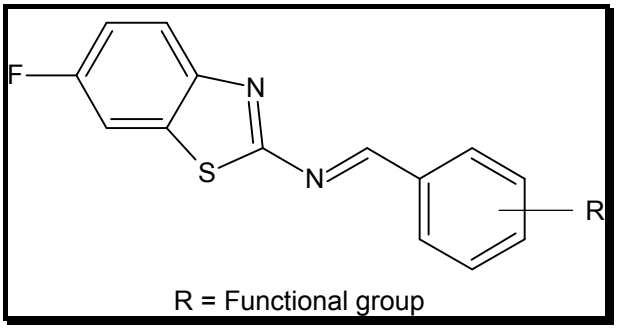


Section 4: Synthesis of Tetrahydropyrimidines



Part 2: Synthesis of Azomethines

This part comprises synthesis of azomethines from benzthiazole amine.



CHAPTER 3

In this chapter, some physicochemical properties have been studied for some **dihydropyrimidinones derivatives (RVG series)** in N, N-dimethylformamide (DMF) and dimethyl sulphoxide (DMSO) solutions of different concentrations at 298.15 K. This chapter divided into six sections.

Section 1: Acoustical studies

In this section, sound velocity of some synthesized compounds (RVG series) in DMF and DMSO solutions of different concentrations were studied at 298.15 K. Further, density and viscosity also have been measured. Using these experimental data, some acoustical parameters were calculated which

are interpreted in terms of solute-solute and solute-solvent interactions in different solutions.

Section 2: Density and Refractive index

Since refractive index is a fundamental physical property of a substance, it is often used to identify a particular substance, confirm its purity, or measure its concentration. In this section, the density and refractive index of compounds of RVG series were measured in DMF and DMSO solutions at 298.15 K. Further, the density of these compounds was also evaluated theoretically and was compared with experimental values. The molar refraction and refractive index of compounds have also been calculated.

Section 3: Conductance

This section deals with the conductance measurement of solutions of compounds of RVG series in DMF and DMSO solutions over a wide range of concentration at 298.15 K. From these experimental values, specific conductance and equivalent conductance for studied compounds was measured.

Section 4: Solubility

The solubility of some derivatives of RVG series compounds in DMF and DMSO were measured by a gravimetrical method at different temperatures (298.15 to 318.15 K) under atmospheric pressure. Further, some thermodynamic parameters such as Gibbs energy, enthalpy and entropy of solutions have been evaluated.

Section 5: Dissociation constants

This section deals with the dissociation constant of compounds of RVG series were studied in DMF-water mixtures at 298.15, 308.15 and 318.15 K.

From the experimental data, some thermodynamic parameters have been evaluated.

Section 6: Thermal Properties

In this section, the thermal properties of some dihydropyrimidinones derivatives were studied by TGA and DSC technique. From this data, various kinetic parameters such as energy of activation, order of degradation, frequency factor and entropy change were evaluated. The stability of various compounds was also determined from these data. Further, the melting point observed by DSC was compared with open capillary method for each derivative.

CHAPTER 4: Biological activity

In the present chapter, antibacterial activity of all the synthesized compounds was studied against some Gram positive and Gram negative bacteria in DMF and DMSO.

Signature of Guide **Signature of Student**

(Dr. Shipra Baluja) **(Ravi V. Gajera)**

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Chapter -1

General Introduction

GENERAL INTRODUCTION

The primary objective of medicinal chemistry is the design and discovery of new compounds that are suitable for use as drugs. This process involves a team of workers from a wide range of disciplines such as chemistry, biology, biochemistry, pharmacology mathematics, medicine and computing, amongst others.

The discovery or design of a new drug requires synthesis of drug, method of administration, development of tests and procedures to establish how it operates in the body and safety assessment. Drug discovery may also require fundamental research into the biological and chemical nature of the diseased state. For this, specialists from various fields including medicinal or organic chemists are needed.

The first rational development of synthetic drugs was carried out by Ehrlich and Hata who produced arsphenamine in 1910 by combining synthesis with reliable biological screening and evaluation procedures[1].

Heterocycles form by far the largest of the classical divisions of organic chemistry and are of immense importance biologically, industrially, and indeed to the functioning of any developed human society. The majority of pharmaceuticals and biologically active agrochemicals are having heterocyclic nucleus.

The heterocyclic compounds occupy a key position in the area of drugs and pharmaceuticals. Almost 80% of the drugs in clinical use are based on heterocyclic constitution because they have specific chemical reactivity.

Majority of drugs being introduced in pharmacopeias in recent years are heterocyclic compounds. A wide variety of drugs such as chlordiazepoxide (tranquillizer)[2, 3], imipromine (antidepressant)[4], guanethidine (antihypertensive)[5], indapamide (diuretic and antihypertensive)[6,7], ketoprofen[8], fenoprofen and flurbiprofen penicillin[9], cephalosporin[10], norfloxacin[11], streptomycin[12, 13] etc., contain heterocyclic nucleus.

Further, in industries various additives and modifiers having heterocyclic moiety are used. In addition to these, in cosmetics, reprography, information storage, plastics etc. various heterocyclic compounds have been used. Thus, for many recruits to positions in the pharmaceutical industry, a fast introduction to heterocyclic chemistry is a must.

Various plants contain heterocyclic compounds and these compounds are known to be biologically active[14-16]. Some heterocycles are fundamental to life, such as haem derivatives in blood and the chlorophylls essential for photosynthesis[17, 18]. Further, the paired bases found in RNA and DNA are heterocycles[19], sugars that in combination with phosphates[20] (which provide the backbones and determine the topology of these nucleic acids), some dyestuffs of plant origin include indigo blue[21] and a poison strychnine[22], obtained from the plant resin curare etc., contain heterocyclic ring. Pyrrole[23] was detected in the dry distillation of bones and pyridine[24] was also isolated from bone oil.

A heterocyclic nucleus is a ring in which at least one atom is not carbon. Compound containing aromatic heterocyclic nuclei have been known since the earliest studies in organic chemistry. In 1818, Brugnatelli had isolated alloxan by oxidizing of uric acid[25]. Other derivatives of uric acid (purines and pyrimidines) were described by Wohler and Liebig[26].

Taking in view of the applicability of heterocyclic compounds, the present work was undertaken to synthesize some new heterocycles bearing pyrimidine and benzothiazole nucleus.

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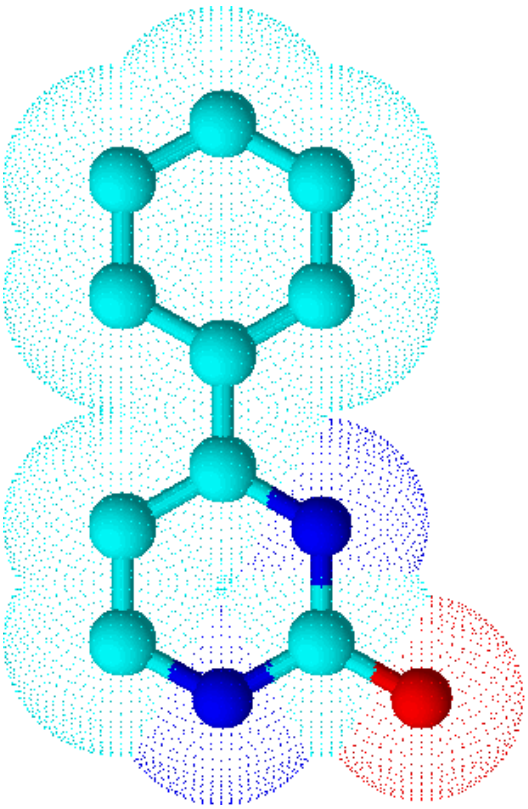
GENERAL REMARKS

1. Melting points were recorded by open capillary method and are uncorrected.
2. Infrared spectra were recorded on SHIMADZU FTIR-8400 (Diffuse reflectance attachment) in the frequency range of 4000-400 cm^{-1} using KBr. Spectra were calibrated against the polystyrene absorption at 1610 cm^{-1}.
3. ^{1}H NMR spectra were recorded on BRUKER AVANCE II 400 spectrometer. Making a solution of samples in DMSO d6 and CDCl3 solvents using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned, and are given in the δ scale.
4. Mass spectra were recorded on SHIMADZU GCMS-QP2010 spectrometer operating at 70 eV using direct injection probe technique.
5. Analytical thin layer chromatography (TLC) was performed on Merck-precoated silica gel-G F254 aluminium plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light.
6. The chemicals used for the synthesis of intermediates and end products were purchased from Spectrochem, Sisco Research Laboratories (SRL), Thomas-Baker, Sd fine chemicals and Loba chemie.
7. Ultrasonic interferometer was carried Mittal Enterprise, New Delhi, Model No. F-81) working at frequency of 2 MHz was used to determine sound velocity, with the uncertainty of 0.01%.
8. The structures and names of all the compounds given in the experimental section were generated using ACD Chemsketch version 12.0.

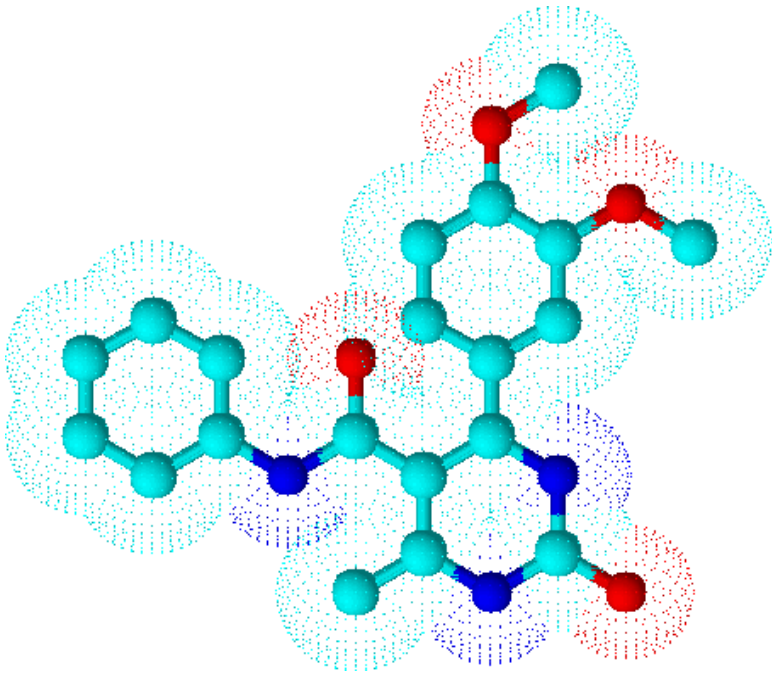
Chapter -2

Synthesis and Characterization



Part-1

Synthesis of Pyrimidine Derivatives



Section-I

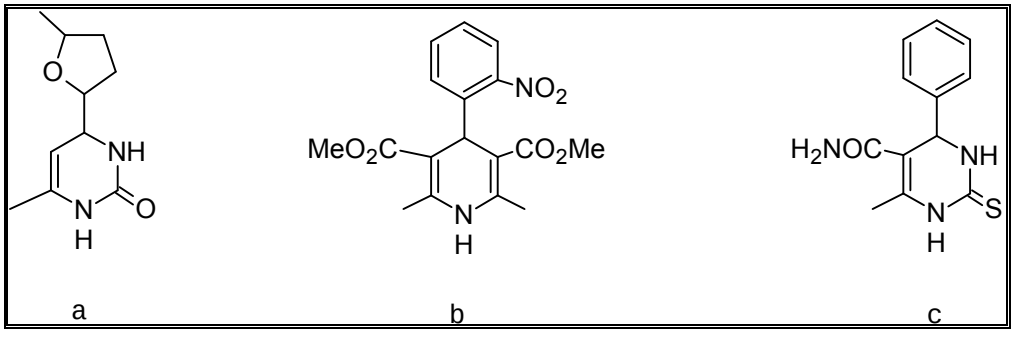
Synthesis of Dihydropyrimidinones

INTRODUCTION

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry. Over the last decade, industrial and academic researchers have made such powerful MCR strategies into one of the most efficient and cost-effective tools for combinatorial and parallel synthesis.[1] One prominent MCR that produces an interesting class of nitrogen heterocycles is the venerable Biginelli dihydropyrimidine synthesis.[2] Thus, multicomponent reaction is of much importance due to excellent pharmacological properties of dihydropyrimidines.

The nitrogen containing heterocycles are an important class of compounds, contributed to the society from biological and industrial point of view which helps to understand life processes[3]. Dihydropyrimidines are known to possess therapeutic and pharmacological properties[2] such as in vitro activity against unrelated DNA and RNA, viruses including polio herpes viruses, diuretic, antitumor, anti HIV, cardiovascular[4].

Several alkaloids isolated from marine sources exhibit interesting biological properties[5, 6]. These isolated alkaloids contain the dihydropyrimidine unit. Some of these isolated marine alkaloids containing dihydropyrimidinones (eg. betzelladine alkaloids) are known to be a potent HIVgp-120-CD4 inhibitors[7-9]. The compound nitractin(A) i.e., a dihydropyrimidine derivative exhibited anti viral activity[10]. 4-Aryl dihydropyrimidines *e.g*. nifedipine (B) are used as calcium channel modulars, which is also used for the treatment of cardiovascular diseases[11]. Some of the analogues were screened as anti tumor agents. Pyrimidine -5-carboxamide of type (C) was reported to possess anti carcinogenic activity, anti inflammatory[12] and analgesic[13] activities.



There are various methods for the synthesis of dihydropyrimidines. Many researchers have reported the use of different catalysts in the synthesis of dihydropyrimidines. Recently, various new methods for the synthesis of these compounds have been developed to improve the efficiency of the Biginelli reaction, such as use of heteropoly acids[14], $CuCl_2$-H_2O[15], l-proline[16], praseodymium methanesulfonate[17], chloroacetic acid[18], etidronic acid[19], zinc methanesulfonate[20] etc. The search for the new, readily available, and green catalysts is still being actively pursued.

Because of the great potential of room-temperature ionic liquids as environmentally benign media for catalytic processes, much attention has currently been focused on the organic reactions catalyzed with or in ionic liquids. Various organic reactions promoted with acid-base catalysts are now done in ionic liquids.[21] In recent years, the acidic ionic liquids have also been used as catalysts for the Biginelli reaction[22-24]. Reddy and coworker[25] have reported the synthesis of dihydropyrimidines by using Zirconium chloride catalyst. Guo and salehi[26] have synthesized dihydropyrimidinones using magnesium bromide as a catalyst under solvent free condition.

Very recently, for novel Biginelli-like scaffold syntheses[27], the common open-chain b-dicarbonyl compounds has been used to cyclic b-diketones[28], b-ketolactones[29], cyclic b-diesters[30] or b-diamides [31, 32], benzocyclic ketones and a-ketoacids[33]. These reactions suffer from limitations such as low yields, very long reaction times, harsh reaction conditions and unrecoverable strong acids.

Thus, owing to the biological importance of dihydropyrimidinone derivatives, the present chapter describes the synthesis and characterization of some 1,4-dihydropyrimidinone derivatives.

EXPERIMENTAL

Synthesis of 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

[A] Synthesis of 3, 4-dimethoxybenzaldehyde:

An aqueous solution (20 ml) of vaniline (0.01M) was refluxed at 100 ^{0}C for half an hour with stirring. To this solution, few drops of NaOH and 2 ml of dimethylsulphate (DMS) were added slowly and again the reaction mixture was stirred with refluxed for 3 to 3.5 hrs. Then, diethyl ether was added to the reaction mixture and solvent was allowed to evaporate. The crude product was isolated and crystallized from absolute ethanol.

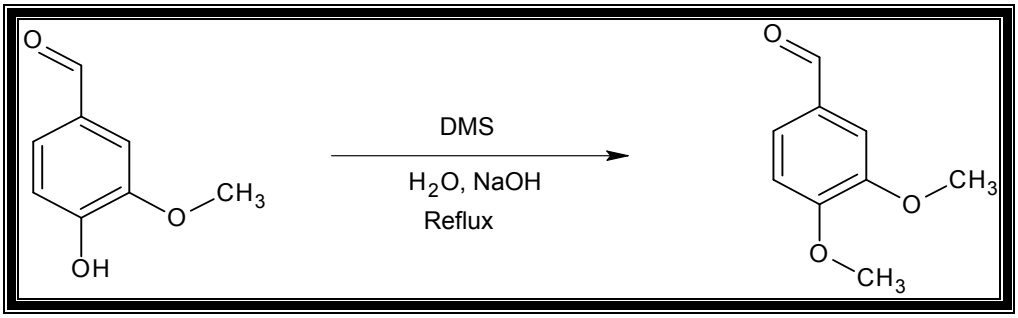
[B] Synthesis of 3-oxo-N-phenylbutanamide:

A mixture of substituted aniline (0.01 M) and ethylacetoacetate (0.01 M) in 40 ml toluene was refluxed for 12 hours in presence of few drops of slurry of NaOH in water. The reaction was monitoring with TLC. The excess toluene was distilled out and the reaction mixture was taken in hexane and stirred with glass rod. The products were isolated in hexane and filtered, dried. The crude product was taken in aqueous NaOH solution and neutralized with dilute HCl. The recrystalisation was done in ethanol.

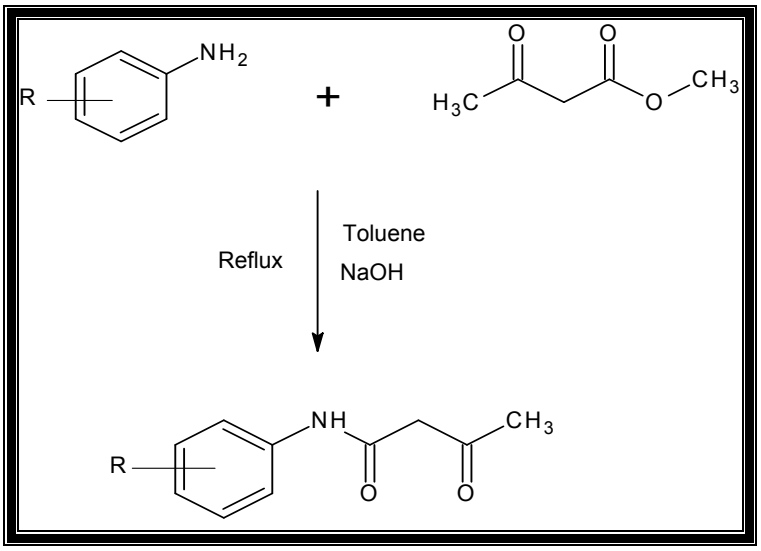
[C] Synthesis of 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide:

A mixture of 3, 4 dimethoxy aldehyde (0.01 M), substituted diketones (0.01 M) and urea (0.015 M) in methanol was refluxed for 12 hours in presence of few drops of concentrated HCl as catalyst. The product was isolated and crystallized from ethanol. All the synthesized compounds were recrystallized from ethanol.

[A] Synthesis of 3, 4-dimethoxybenzaldehyde:



[B] Synthesis of 3-oxo-N-phenylbutanamide:



[C] Synthesis of 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide:

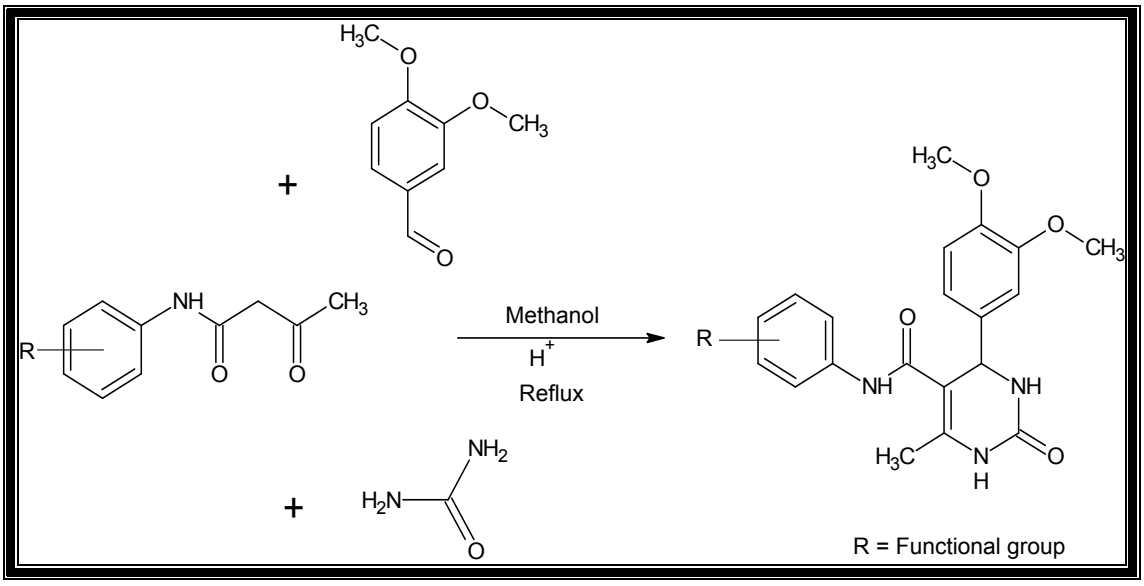


Table 2.1.1: Physical constants of Dihydropyrimidenons.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. °C	Yield %
1	**RVG-1**	4-OCH_3	$C_{21}H_{23}N_3O_5$	397	0.61	168	53
2	**RVG-2**	4-CH_3	$C_{21}H_{23}N_3O_4$	381	0.54	152	57
3	**RVG-3**	4-Cl	$C_{20}H_{20}ClN_3O_4$	401	0.49	179	46
4	**RVG-4**	2- CH_3	$C_{21}H_{23}N_3O_4$	381	0.47	182	62
5	**RVG-5**	3- OCH_3	$C_{21}H_{23}N_3O_5$	397	0.54	164	45
6	**RVG-6**	4-F	$C_{20}H_{20}FN_3O_4$	385	0.71	160	59
7	**RVG-7**	2,5 – di Cl	$C_{20}H_{19}Cl_2N_3O_4$	436	0.37	171	72
8	**RVG-8**	3-Cl	$C_{20}H_{20}ClN_3O_4$	401	0.62	198	62
9	**RVG-9**	3,4 – di Cl	$C_{20}H_{19}Cl_2N_3O_4$	436	0.66	169	77
10	**RVG-10**	3-Cl, 4-F	$C_{20}H_{19}ClFN_3O_4$	419	0.52	145	78

*Chloroform : Methanol: 9:1

The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized 1,4-dihydropyrimidinone derivatives are given in Table 2.1.1. The characterization was done by IR, ^{1}H NMR and mass spectra.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 Spectrophotometer in the frequency range of 4000-400 cm^{-}1 by KBr powder method. Figure 2.1.1 shows IR spectra of RVG-5. The IR spectral data for RVG-5 is given in Table 2.1.2. The spectral data for all other compounds are reported in Table 2.1.3.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2.1.2 shows NMR spectra of RVG-5. The spectral data for RVG-5 is given in Table 2.1.4.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 2.1.3 shows mass spectra of RVG-5.The proposed mass fragmentation of the same compound is also given in Scheme 2.1.1.

Figure 2.1.1: IR spectra of 4-(3,4-dimethoxyphenyl)-N-(2-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RVG-5).

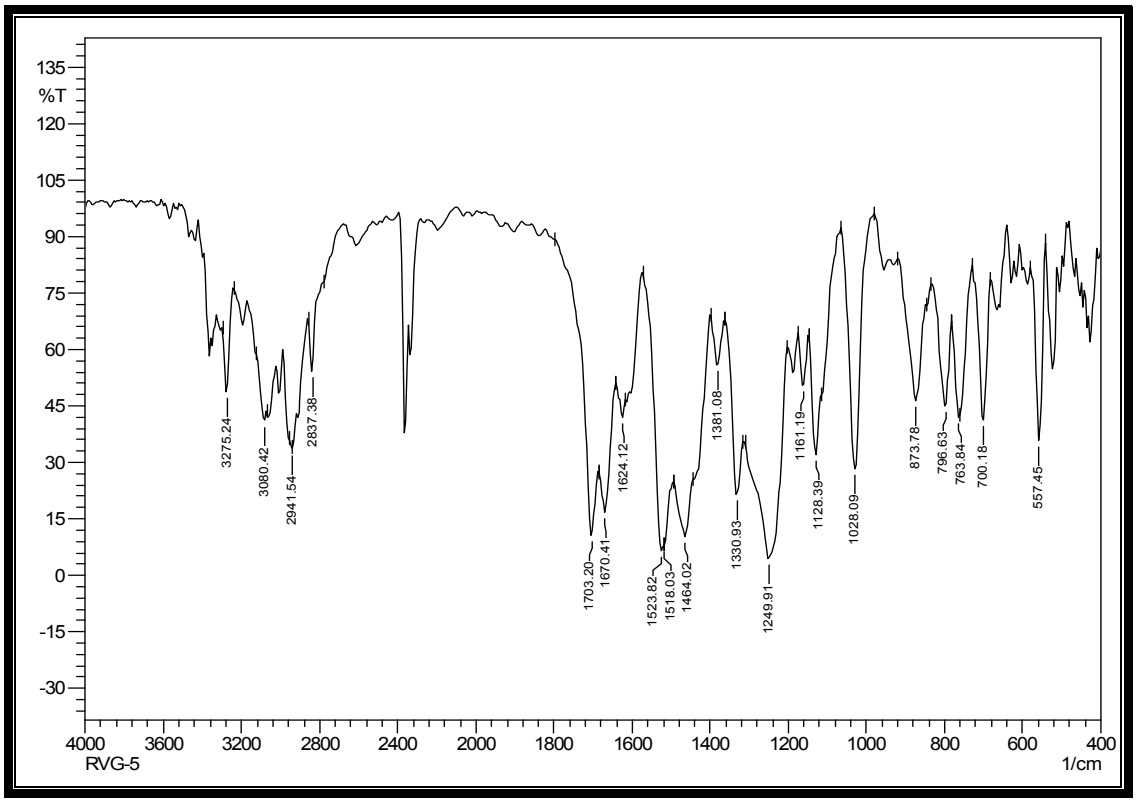


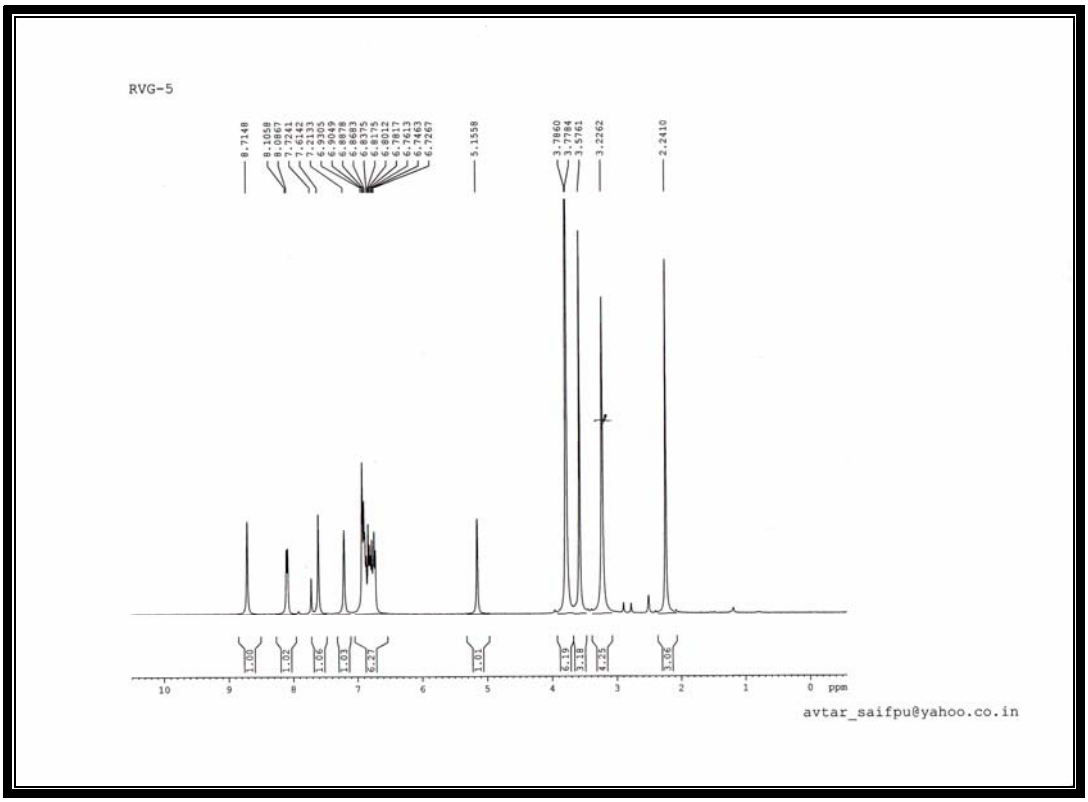
Table 2.1.2: IR spectral data of 4-(3,4-dimethoxyphenyl)-N-(2-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (RVG-5).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported
Alkane	C-H str. (asym.)	2941.54	2975-2900
	C-H str. (sym.)	2837.38	2880-2810
	C-H def. (asym.)	1454.02	1480-1435
	C-H def. (sym.)	1330.93	1985-1350
Aromatic	C-H str.	3080.42	3100-3000
	C=C str.	1518.03	1585-1480
	C-H i.p. def.	1128.39	1125-1090
	C-H o.o.p. def.	796.63	860-810
Ketones	C=O str.(cyclic)	1703.20	1740-1680
	C=O str. (alip.)	1670.41	1710-1650
Nitrogen	C-N str.	1249.91	1350-1200
	N-H str.	3275.24	3400-3200
	N-H def.	1523.82	1650-1500
Ether	C-O-C str. (asym.)	1161.19	1400-1000
	C-O-C str. (sym.)	1028.09	1075-1020

Table 2.1.3: IR spectral data of synthesized 1,4-Dihydropyrimidinones.

Compounds	*IR ν, (cm^{-1})*					
	C=O (cyclic)	C=O (alip.)	N-H (Str.)	C=C (Str.)	C-H (asym.)	R
RVG-1	1710.27	1674.33	3342.20	1517.61	2912.31	1145.12
RVG-2	1712.34	1674.38	3294.16	1516.54	2935.28	2879.30
RVG-3	1711.30	1676.46	3279.17	1539.21	2946.46	759.59
RVG-4	1716.16	1681.67	3261.14	1518.08	2943.42	2839.50
RVG-6	1715.24	1664.59	3321.26	1537.03	2953.27	689.46
RVG-7	1722.22	1673.51	3267.20	1529.55	2955.21	749.12
RVG-8	1720.08	1659.52	3309.49	1520.43	2912.55	762.20
RVG-9	1711.09	1666.45	3261.34	1514.37	2967.24	758.12
RVG-10	1707.10	1678.51	3286.51	1502.36	2972.33	671, 754

Figure 2.1.2: ^{1}H NMR spectra of 4-(3,4-dimethoxyphenyl)-N-(2-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (RVG-5).



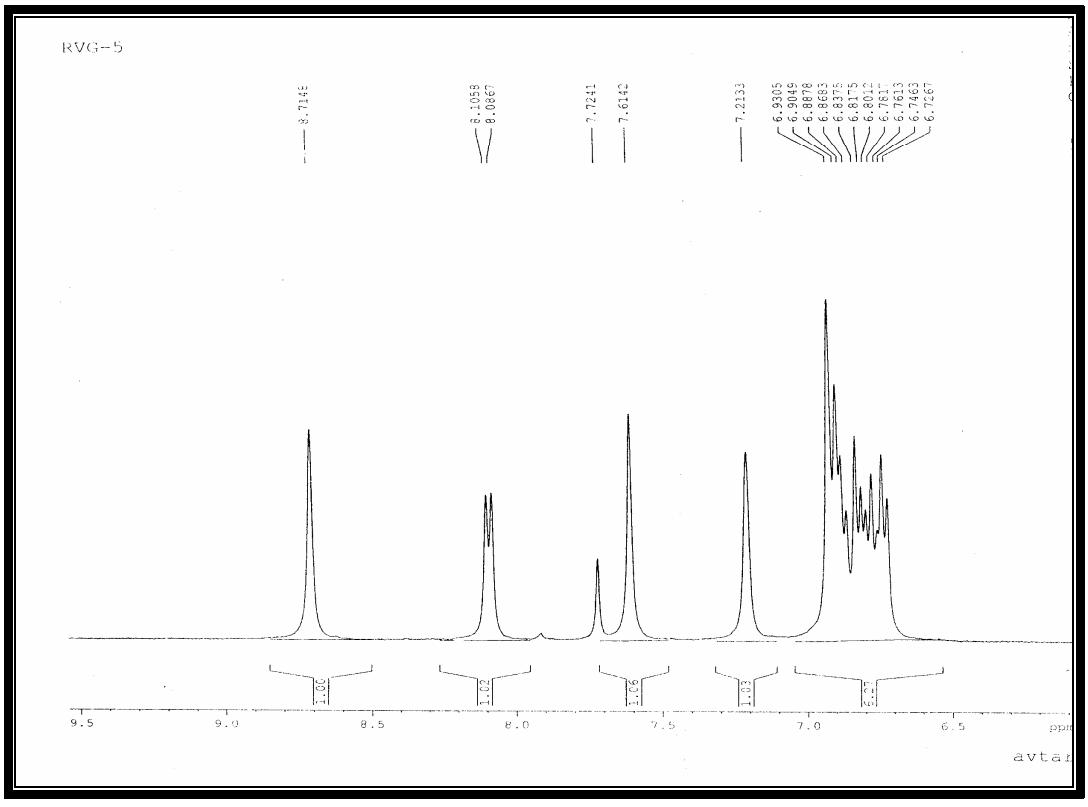
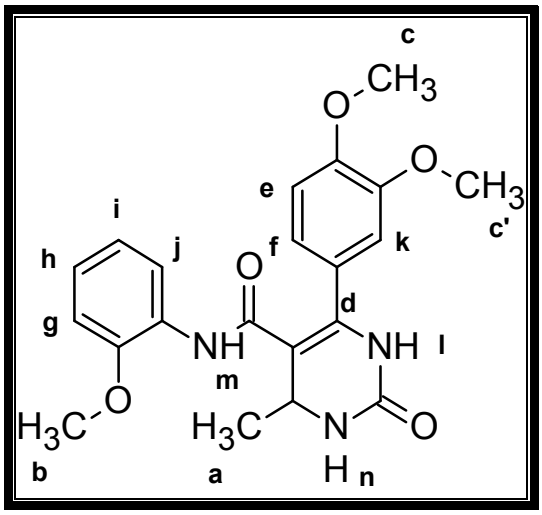
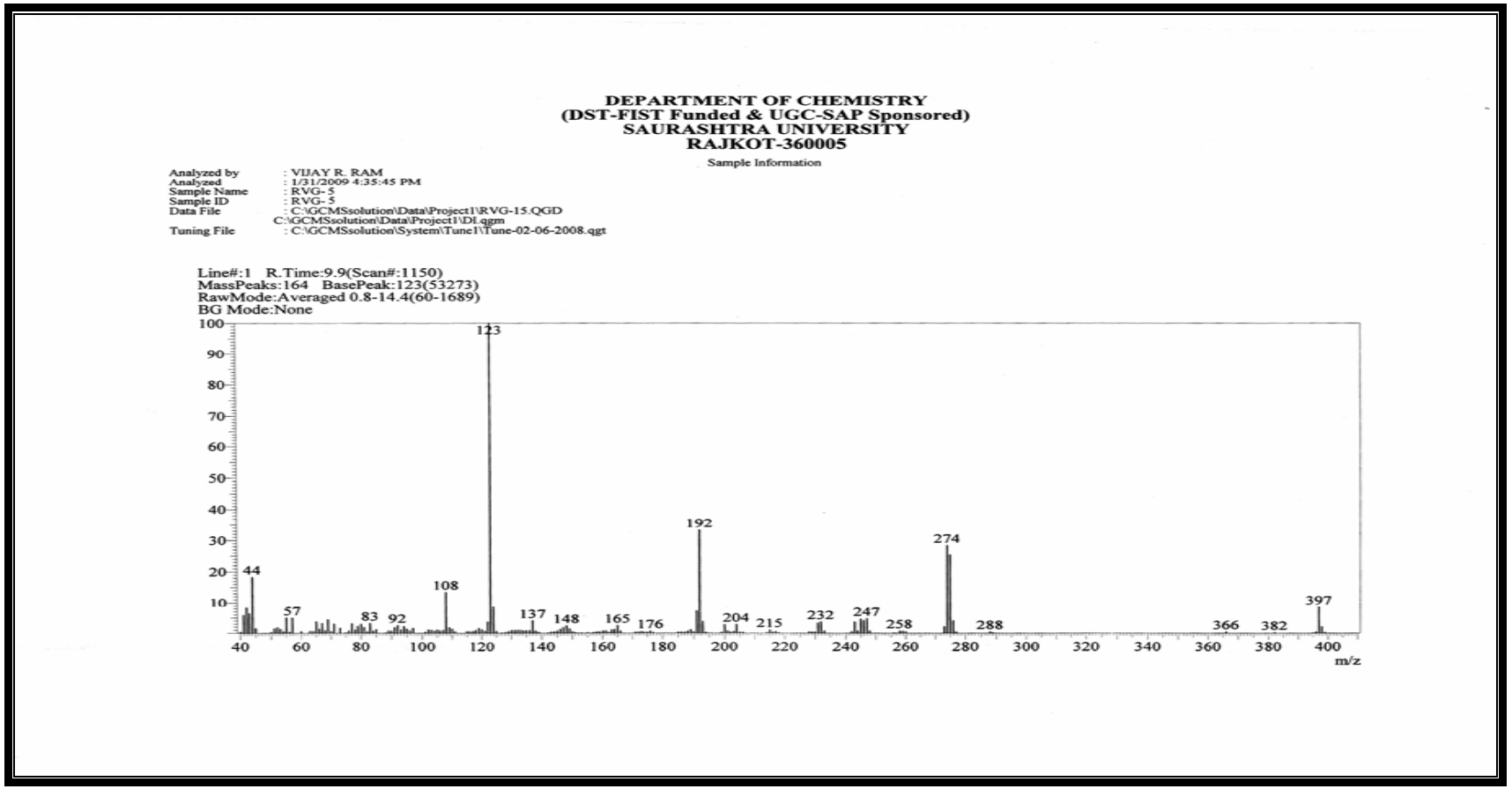


Table 2.1.4: ^{1}H NMR spectral data of 4-(3,4-dimethoxyphenyl)-N-(2-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (RVG-5).

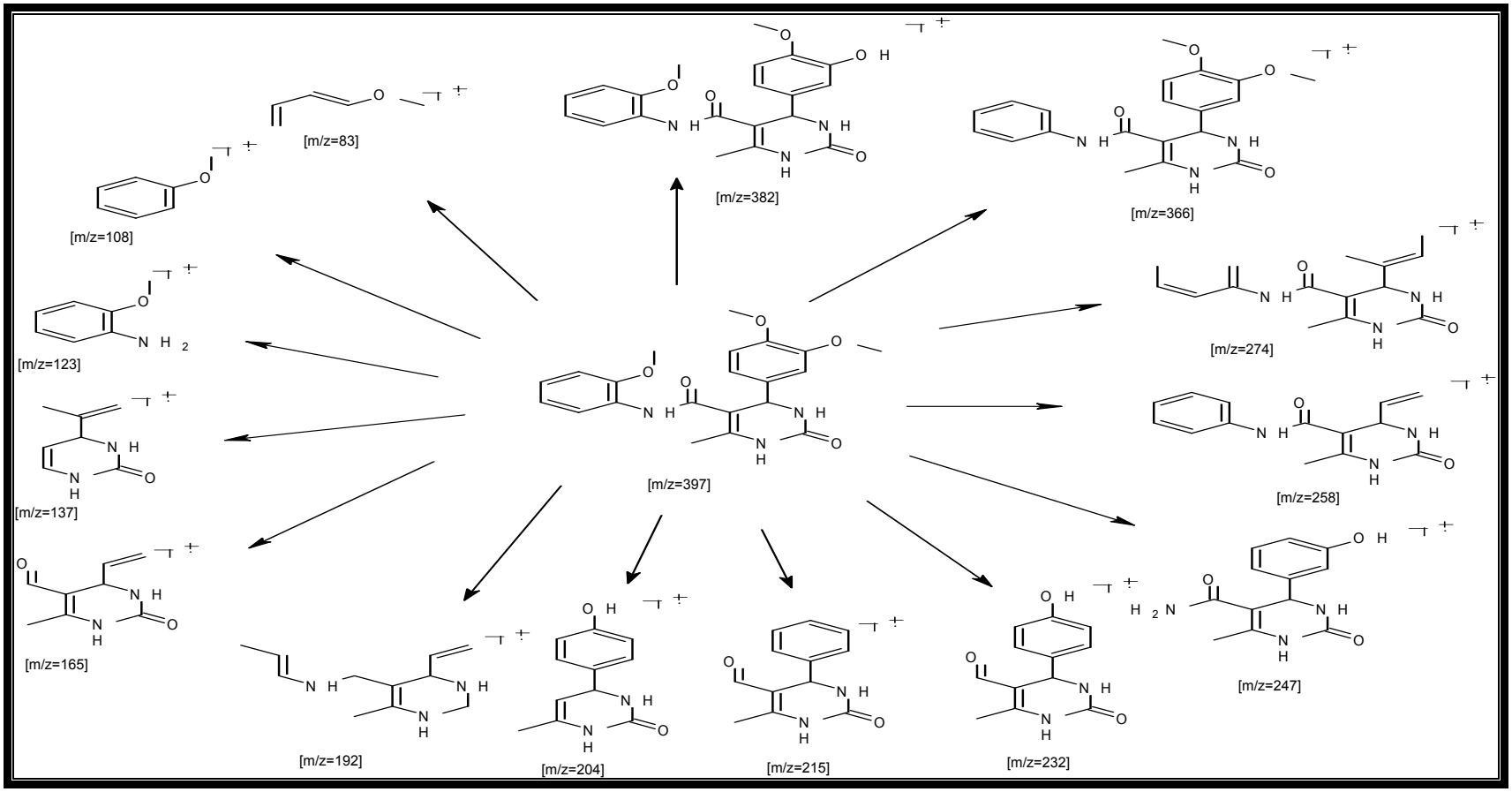


Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	2.24	3H	singlet	-C$\underline{H}_a$	-
2	3.57	3H	singlet	-OC$\underline{H}_b$	-
3	3.87	6H	singlet	-OC$\underline{H}_{cc'}$	-
4	5.57	1H	singlet	H_d	-
5	6.72-6.93	6H	multiplat	-Ar-H_{e-j}	-
6	7.21	1H	singlet	-Ar-H_k	-
7	7.61	1H	singlet	-NH_l	-
8	8.08	1H	singlet	-NH_m	-
9	8.71	1H	singlet	-NH_n	-

Figure 2.1.3: Mass spectra of 4-(3,4-dimethoxyphenyl)-N-(2-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (RVG-5).



Scheme 2.1.1: Proposed mass fragmentation of 4-(3,4-dimethoxyphenyl)-N-(2-methoxyphenyl)-6-methyl-2-oxo 1,2,3,4-tetrahydropyrimidine-5-carboxamide (RVG-5).



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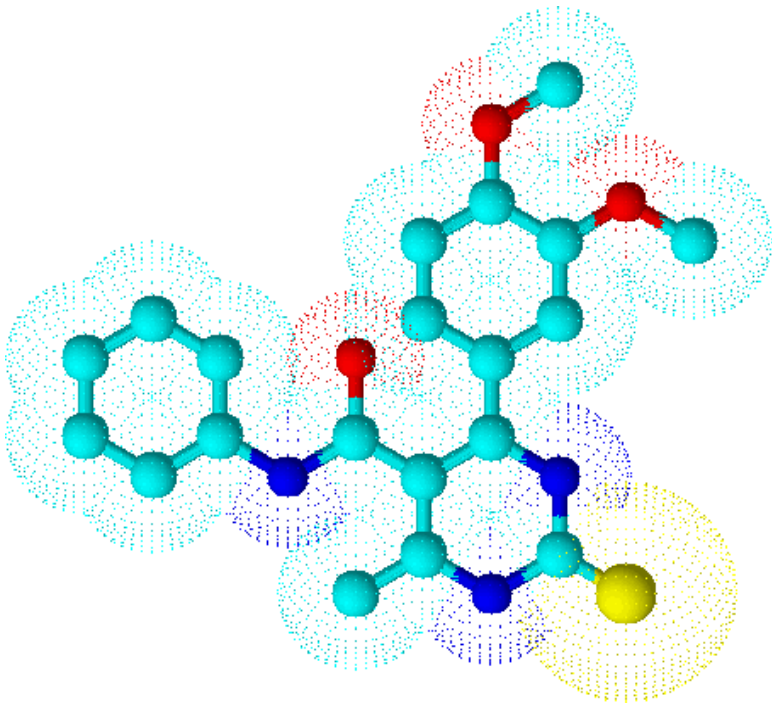


Section-II

Synthesis of Dihydropyrimidinethiones

INTRODUCTION

The chemistry of pyrimidinethiones and its derivatives have been studied since past century due to their pharmacological association with diverse pharmacological properties. Pyrimidine was first isolated by Gabriel and Colman in 1899. Though pyrimidine itself does not exist in nature but substituted pyrimidines containing pyrimidine moiety are found as a part of more complex systems and are widely distributed.

The synthesis of dihydropyrimidinethiones derivatives by the Biginelli reaction is important because of their pharmacological profiles[1–7]. Further, various fused bicyclic systems can also be developed from this precursor[8]. Various modified building blocks, e.g. β-ketoesters, ureas/thioureas, and aldehydes, are used to synthesize molecules with targeted substitutions on a basic skeleton. A large number of catalysts[9–15] are reported to catalyze the reaction efficiently and to provide higher yields. Different methods of synthesis, e.g., microwave-assisted synthesis[16-18], solid phase synthesis[19], and use of ionic liquids[20], have also been investigated.

The first primary synthesis of pyrimidinethione derivatives from aliphatic fragments was carried out by Frankland and Kolbs in 1848. Since then, many distinct primary synthesic methods have been devised.

Pyrimidinethiones represent one of the most active class of compounds possessing a wide spectrum of biological activities, such as antiviral and antitumor[21, 22], anti-inflammatory and analgesic[23], antifilarial[24], anticancer and herbicidel[25, 26], antineoplastic[27], anti HIV[28], antitubercular[29], antagonist[30] antimicrobial[31, 32] antibacterial[33] etc.

Abdel-Rahman et al.[34] have synthesized pyrimidinethione derivatives and reported them as potent antimicrobial agent. Recently, Kern et al.[35] have reported the activity against orthopoxvirus infection of pyrimidinethione derivatives. Liu and co-workers36 have reported the highly enantioselective organocatalytic thiopyrimidines. The inhibitory activities against HIV virus of some modified thiopyrimidine nucleoside have also been reported[37]. The antimicrobial activity of some pyrimidinethiones has also been studied[38, 39].

Thus, the important role played by pyrimidinethiones nucleous for various physiological activities prompted us to synthesis pyrimidinethiones derivatives.

EXPERIMENTAL

Synthesis of 4-(3,4-dimethoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

[A] Synthesis of 3, 4-dimethoxybenzaldehyde:

An aqueous solution (20 ml) of vaniline (0.01M) was refluxed at 100 ^{0}C for half an hour with stirring. To this solution, few drops of NaOH and 2 ml of dimethylsulphate (DMS) were added slowly and again the reaction mixture was refluxed for 3 to 3.5 hrs with stirring. Then, diethyl ether was added to the reaction mixture and solvent was allowed to evaporate. The crude product was isolated and crystallized from absolute ethanol.

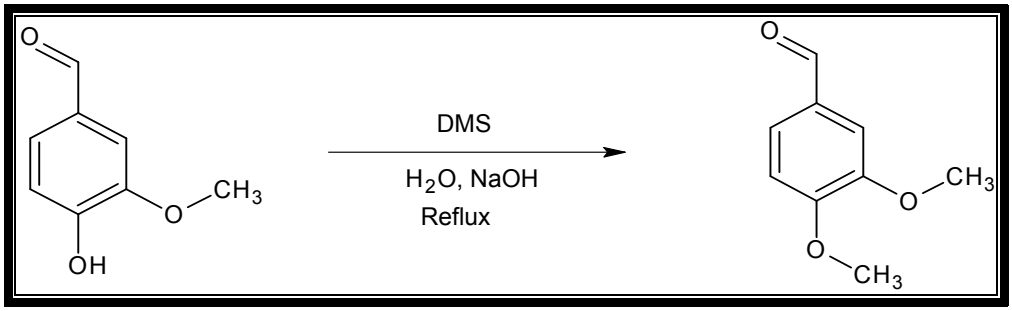
[B] Synthesis of 3-oxo-N-phenylbutanamide:

A mixture of substituted aniline (0.01 M) and ethylacetoacetate (0.01 M) in 40 ml toluene was refluxed for 12 hours in presence of few drops of slurry of NaOH in water. The reaction was monitoring with TLC. The excess toluene was distilled out and the reaction mixture was taken in hexane and stirred with glass rod. The products were isolated in hexane and filtered, dried. The crude product was taken in aqueous NaOH solution and neutralized with dilute HCl. The recrystalisation was done in ethanol.

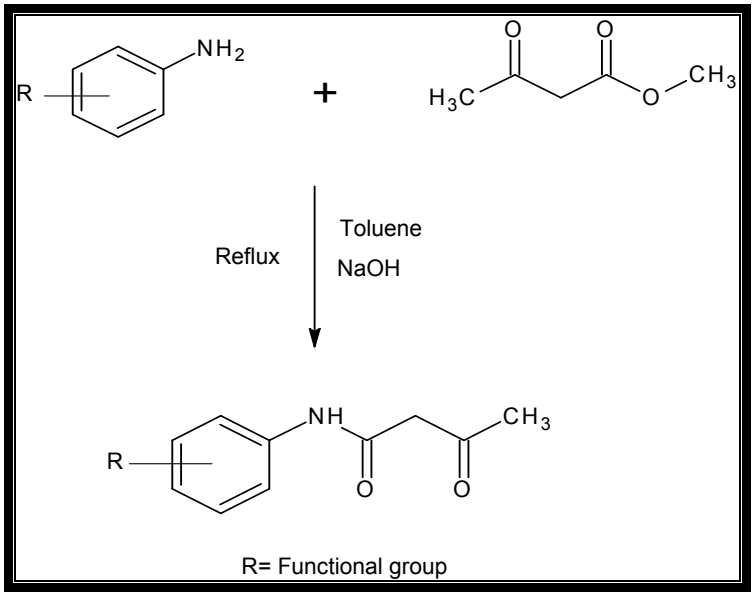
[C] Synthesis of 4-(3,4-dimethoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide:

A mixture of 3, 4 dimethoxy aldehyde (0.01 M), 3-oxo-N-phenylbutanamide (0.01 M) and thiourea (0.012 M) in methanol was refluxed for 12 hours in presence of few drops of concentrated HCl as catalyst. The product was isolated and crystallized from ethanol. All the synthesized compounds were recrystallized from ethanol.

[A] Synthesis of 3, 4-dimethoxybenzaldehyde:



[B] Synthesis of 3-oxo-N-phenylbutanamide:



[C] Synthesis of 4-(3,4-dimethoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide:

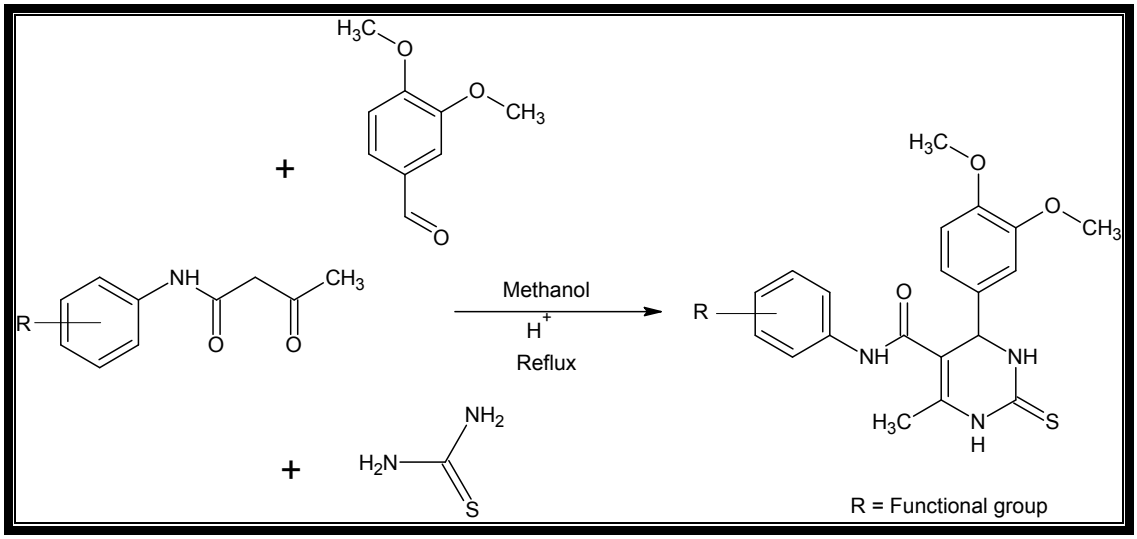


Table 2.2.1: Physical constants of Dihydropyrimidenethiones.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. ^oC	Yield %
1	**SRG-1**	4-OCH_3	$C_{21}H_{23}N_3O_4S$	413	0.49	211	63
2	**SRG-2**	4-CH_3	$C_{21}H_{23}N_3O_3S$	397	0.53	194	56
3	**SRG-3**	4-Cl	$C_{20}H_{20}ClN_3O_3S$	417	0.46	224	66
4	**SRG-4**	2- CH_3	$C_{21}H_{23}N_3O_3S$	397	0.49	232	61
5	**SRG-5**	3- OCH_3	$C_{21}H_{23}N_3O_4S$	413	0.62	215	75
6	**SRG-6**	4-F	$C_{20}H_{20}FN_3O_3S$	401	0.70	248	59
7	**SRG-7**	2,5 - di Cl	$C_{20}H_{19}Cl_2N_3O_3S$	452	0.59	251	70
8	**SRG-8**	3-Cl	$C_{20}H_{20}ClN_3O_3S$	417	0.82	219	65
9	**SRG-9**	3,4 - di Cl	$C_{20}H_{19}Cl_2N_3O_3S$	452	0.63	263	67
10	**SRG-10**	3-Cl, 4-F	$C_{20}H_{19}ClFN_3O_3S$	435	0.70	201	72

* Chloroform:Methanol:- 9:1

The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized dihydropyrimidinethione derivatives are given in Table 2.2.1. The characterization was done by IR, ^{1}H NMR and mass spectra.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 Spectrophotometer in the frequency range of 4000-400 cm^{-1} by KBr powder method. Figure 2.2.1 shows IR spectra of SRG-1. The IR spectral data for SRG-1 is given in Table 2.2.2. The spectral data for all other compounds are reported in Table 2.2.3.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2.2.2 shows NMR spectra of SRG-1. The spectral data for SRG-1 is given in Table 2.2.4.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 2.2.3 shows mass spectra of SRG-1.The proposed mass fragmentation of the same compound is also given in Scheme 2.2.1.

Figure 2.2.1: IR spectra of 4-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (SRG-1).

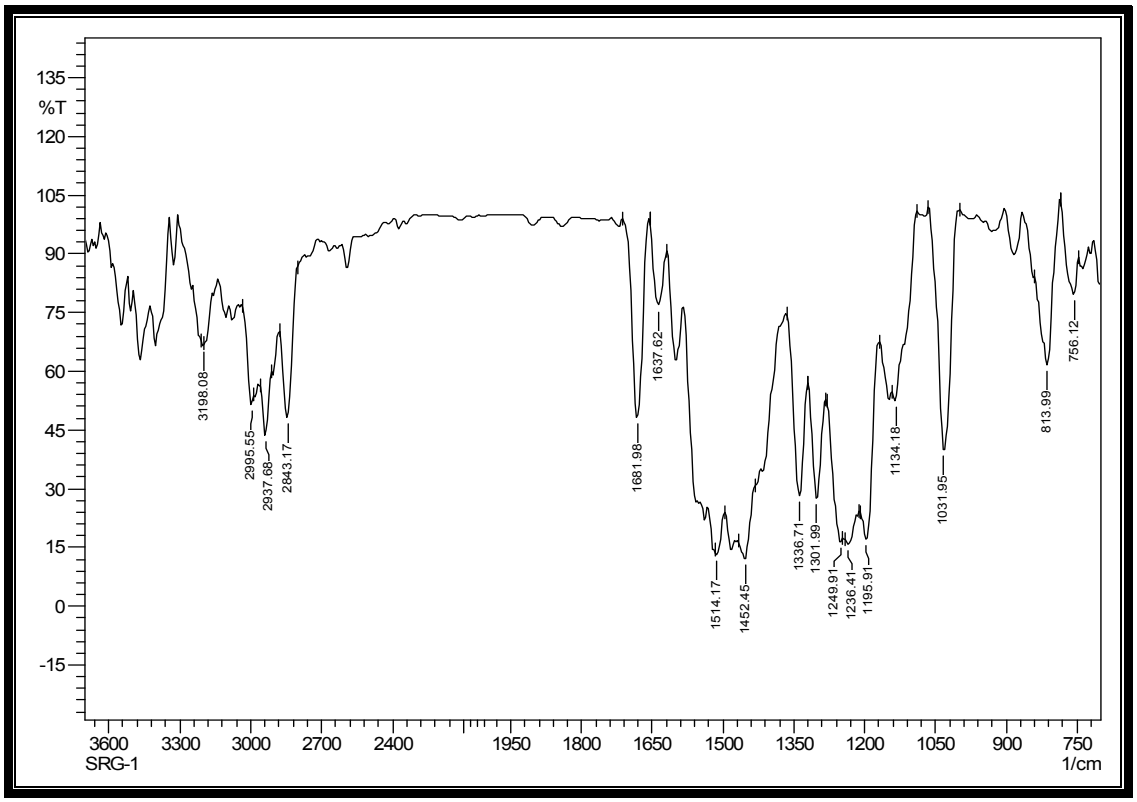


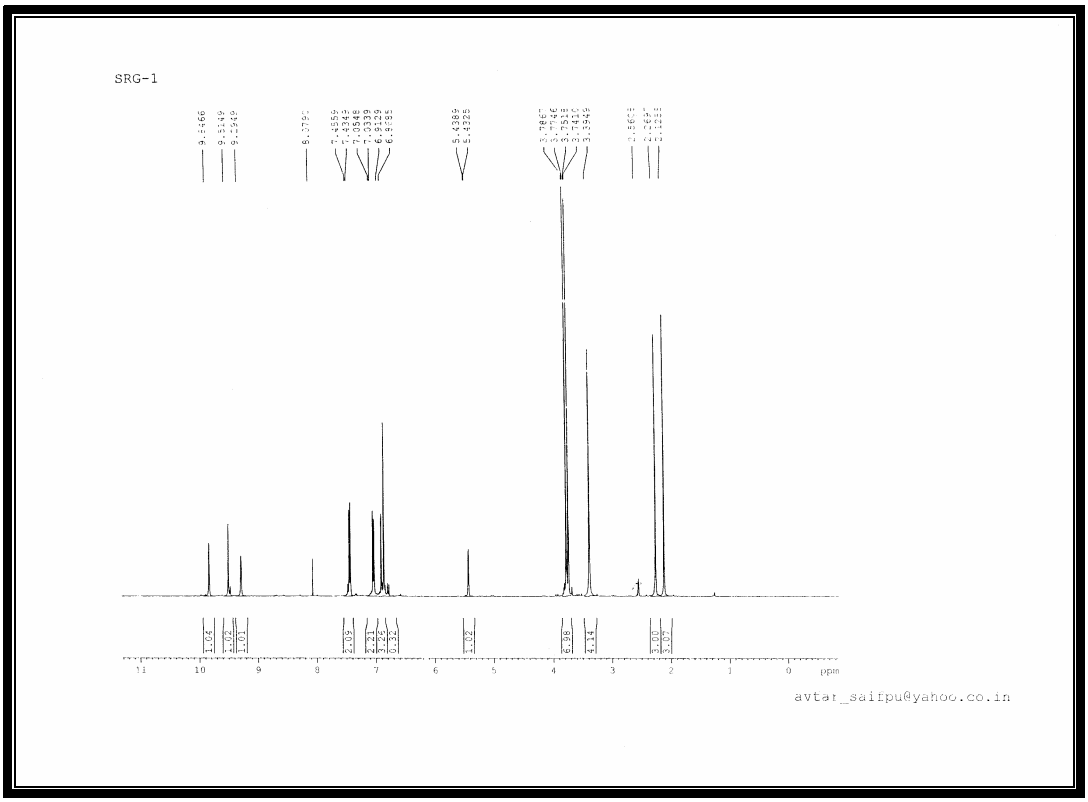
Table 2.2.2: IR spectral data of 4-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (SRG-1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported
Alkane	C-H str. (asym.)	2937.68	2975-2900
	C-H str. (sym.)	2843.17	2880-2810
	C-H def. (asym.)	1452.45	1480-1435
	C-H def. (sym.)	1336.71	1985-1350
Aromatic	C-H str.	2995.55	3100-3000
	C=C str.	1514.17	1585-1480
	C-H i.p. def.	1134.18	1125-1090
	C-H o.o.p. def.	756.12	860-810
Sulfur	C=S str.(cyclic)	1134.18	1050-1200
Ketones	C=O str. (aliphatic)	1637.62	1710-1650
Nitrogen	C-N str.	1301.99	1350-1200
	N-H str.	3350	3400-3200
	N-H def.	1539.	1650-1500
Ether	C-O-C str. (asym.)	1195.91	1400-1000
	C-O-C str. (sym.)	1031.95	1075-1020

Table 2.2.3: IR spectral data of synthesized Dihydropyrimidenethiones.

Compounds	*IR ν, (cm^{-1})*					
	C=S (cyclic)	**C=O (Str.)**	**N−H (Str.)**	**C=C (Str.)**	**C−H (asym.)**	**R**
SRG-2	1146.21	1697.67	3369.11	1516.47	2933.23	2837.22
SRG-3	1189.54	1660.71	3252.27	1500.06	2995.20	734.60
SRG-4	1207.34	1699.39	3314.21	1524.08	2964.37	2861.54
SRG-5	1147.58	1676.24	3217.54	1516.01	2935.48	1145.10
SRG-6	1094.56	1702.57	3285.60	1522.67	2956.54	637.45
SRG-7	1231.79	1688.19	3299.83	1531.57	2961.97	736.19
SRG-8	1161.15	1710.49	3337.70	1529.33	2919.80	764.70
SRG-9	1101.61	1689.56	3250.34	1543.24	2943.45	782.45
SRG-10	1177.57	1691.34	3257.10	1527.49	2964.20	661, 743

Figure 2.2.2: ^{1}H NMR spectra of 4-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (SRG-1).



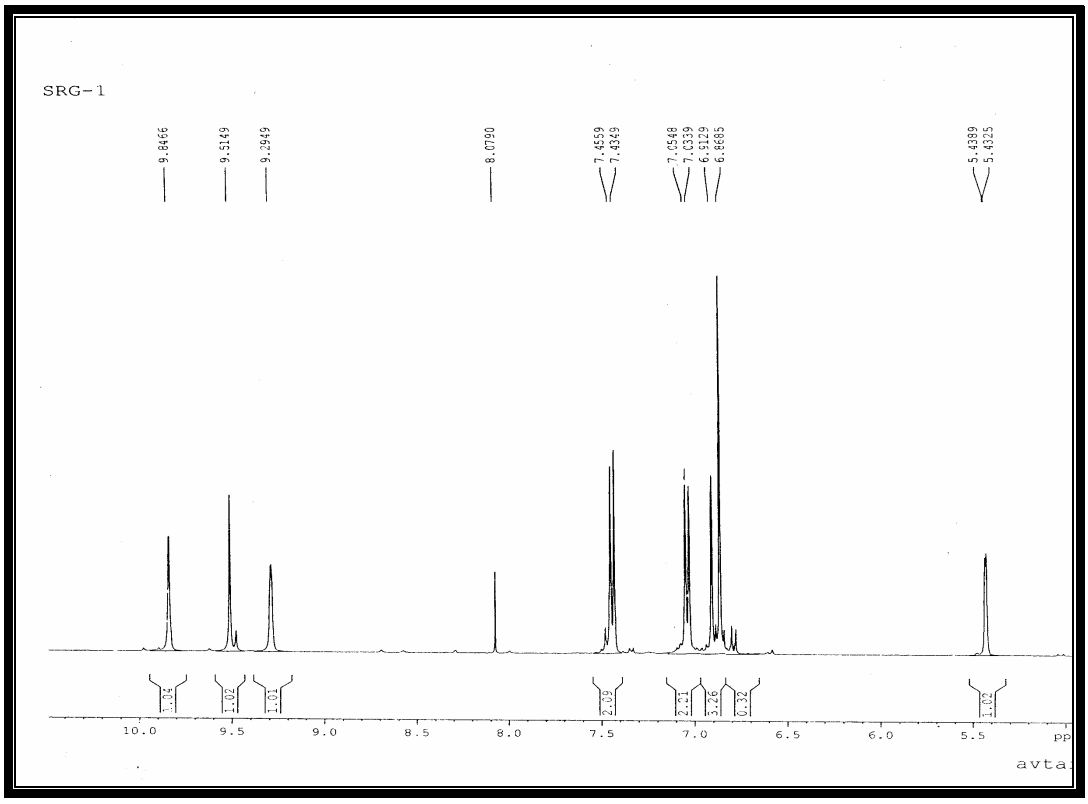
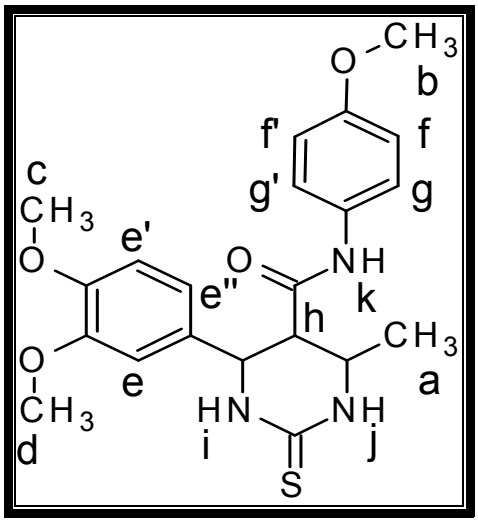
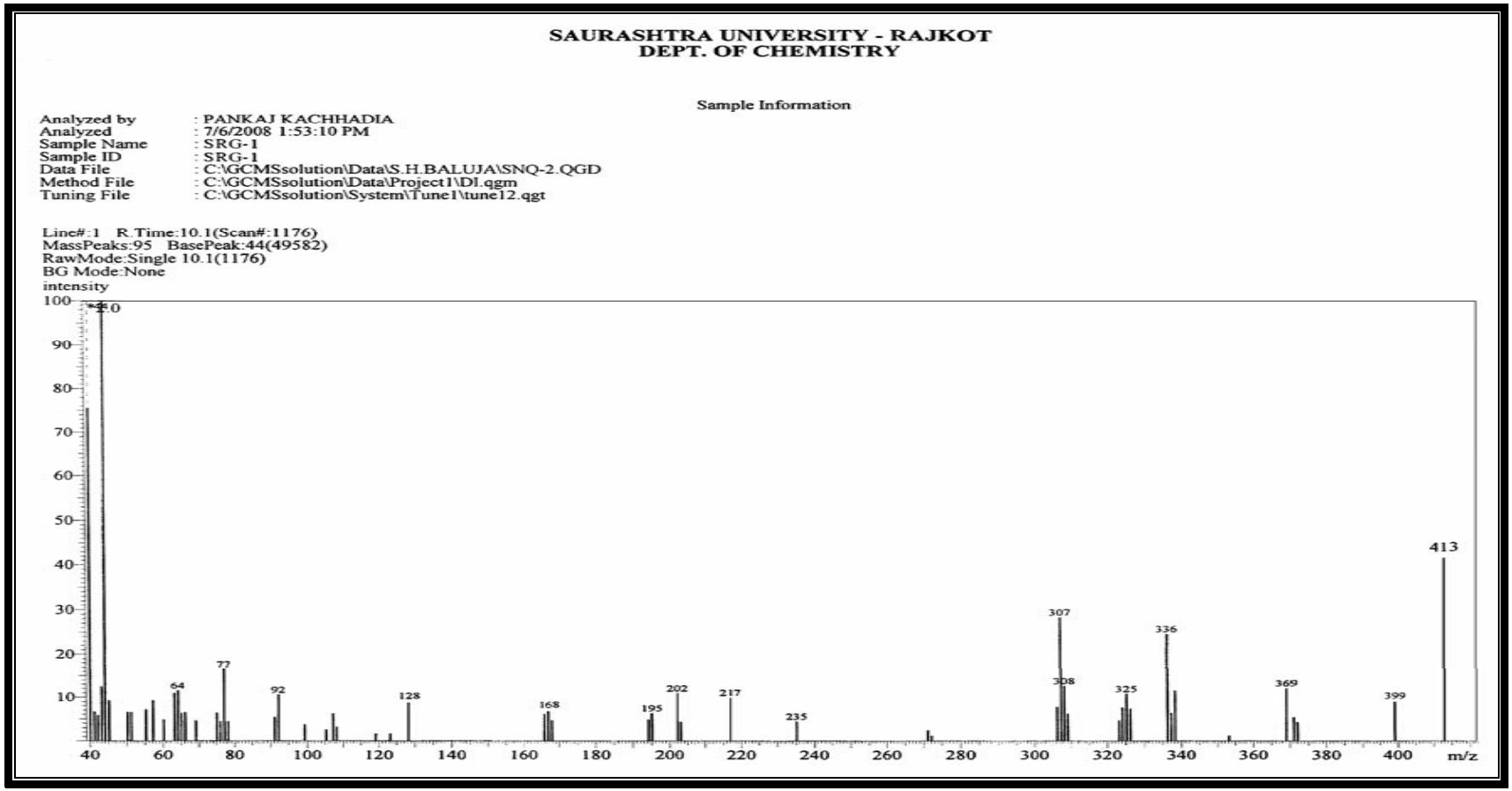


Table 2.2.4: ^{1}H NMR spectral data of 4-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (SRG-1).

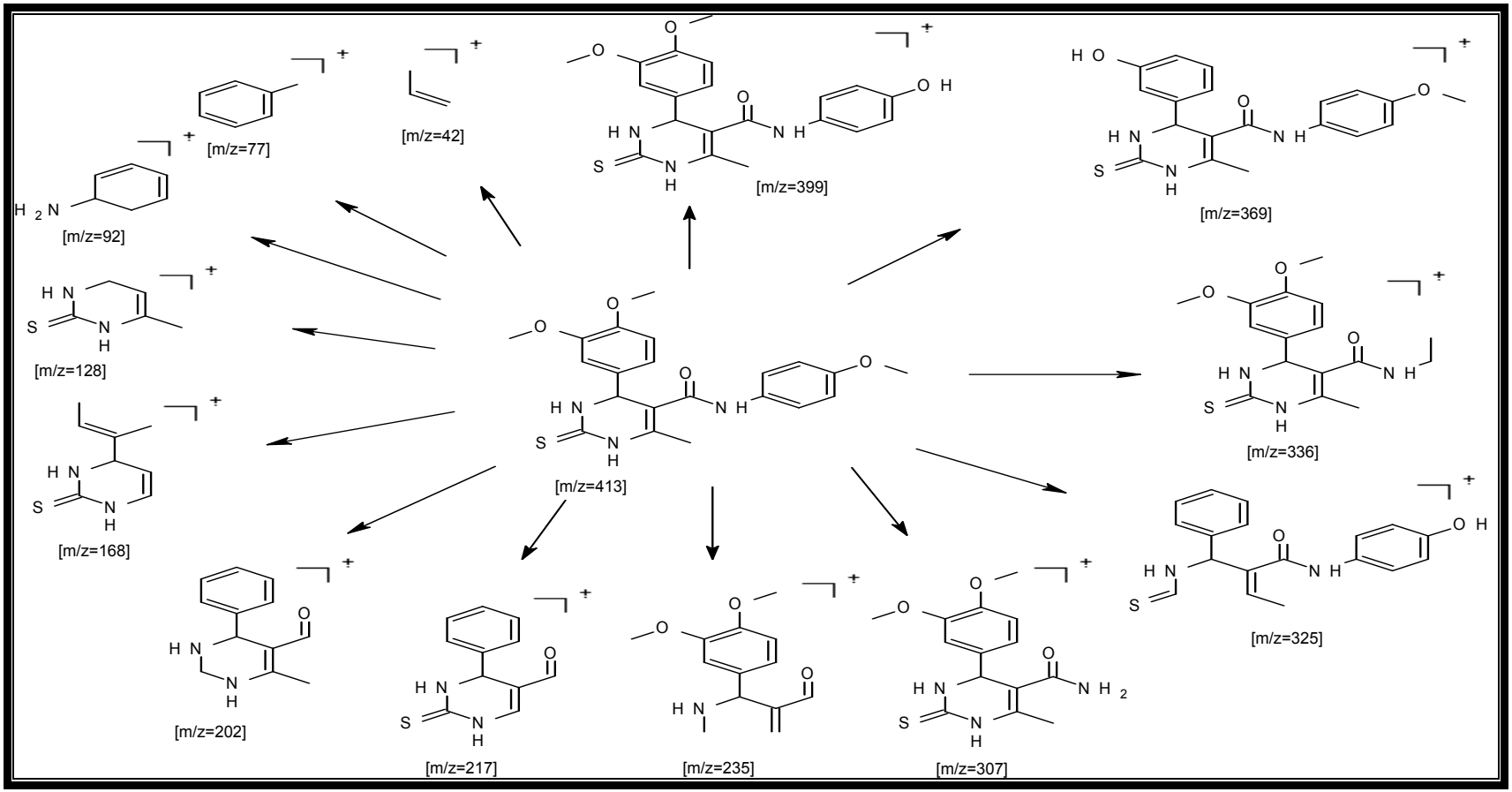


Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	2.12	3H	singlet	-C$\underline{H}_a$	-
2	2.27	3H	singlet	-OC$\underline{H}_b$	-
3	3.74	3H	singlet	-OC$\underline{H}_c$	-
4	3.77	3H	singlet	-OC$\underline{H}_d$	-
5	6.91	3H	multiplet	Ar-$H_{ee'e''}$	-
6	7.03-7.05	2H	doublet	Ar-$H_{gg'}$	
7	7.43-7.45	2H	doublet	Ar-$H_{ff'}$	
8	5.43	1H	singlet	Ar-H_h	-
9	9.29	1H	singlet	Ar-H_i	-
10	9.51	1H	singlet	Ar-H_j	-
11	9.84	1H	singlet	Ar-H_k	-

Figure 2.2.3: Mass spectra of 4-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimi dine-5-carboxamide (SRG-1).



Scheme 2.2.1: Proposed mass fragmentation of 4-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (SRG-1).



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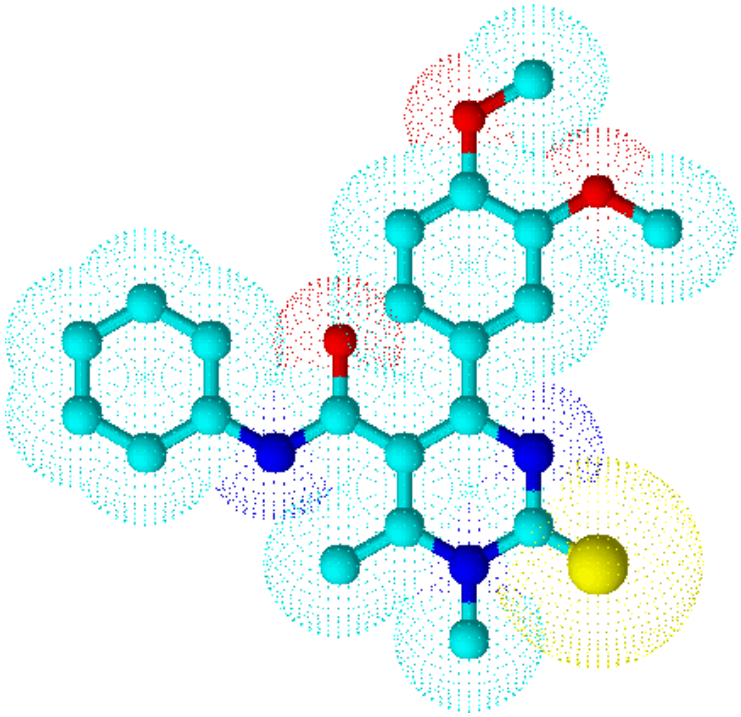
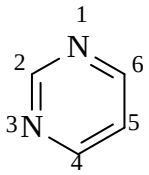


Section-III

Synthesis of N-methylpyrimidines

INTRODUCTION

Pyrimidine (1) is the trivial name for 1,3-diazine: two meta oriental -CH units in benzene have been replaced by nitrogen atom.



1

Pyrimidine derivatives have attracted considerable attention because of their pharmacological properties[1-2], including antiviral[3, 4], antitumor[5], antibacterial[6, 7], and antihypertensive[8, 9], antileukemic[10] effects. Thus, pyrimidines have been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties. In recent years, pyrimidines represent a heterocyclic system with remarkable pharmacological efficiency which shows a very similar pharmacological profile of pyrimidine derivatives calcium channel modulators[11-15] e.g. Nifedipine. Today, such medicines are used for the treatment of cardiovascular diseases[16].

The remarkable biological activities of pyrimidine ring are due to structure similarity to purine RNA and DNA structures[17]. e.g. uracil, thiamine. Various workers have reported the synthesis of 1-methyl pyrimidine and studied their biological activity.

Thus, due to biological potential of the N-methyl pyrimidines, the present work was undertaken to synthesize some novel N-methyl pyrimidine derivatives.

EXPERIMENTAL

Synthesis of 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide.

[A] Synthesis of 3, 4-dimethoxybenzaldehyde:

As per Section - I [A].

[B] Synthesis of 3-oxo-N-phenylbutanamide:

As per Section – I [B].

[C] Synthesis of 6-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RDV-1):

A mixture of 3, 4 dimethoxy aldehyde (0.01 M), 3-oxo-N-phenylbutanamide (0.01 M) and N-methylurea (0.012 M) in methanol was refluxed for 12 hours in presence of few drops of con. HCl as catalyst. The product was isolated and crystallized from ethanol. All the synthesized compounds were recrystallized from ethanol.

REACTION SCHEME

Scheme [c]:

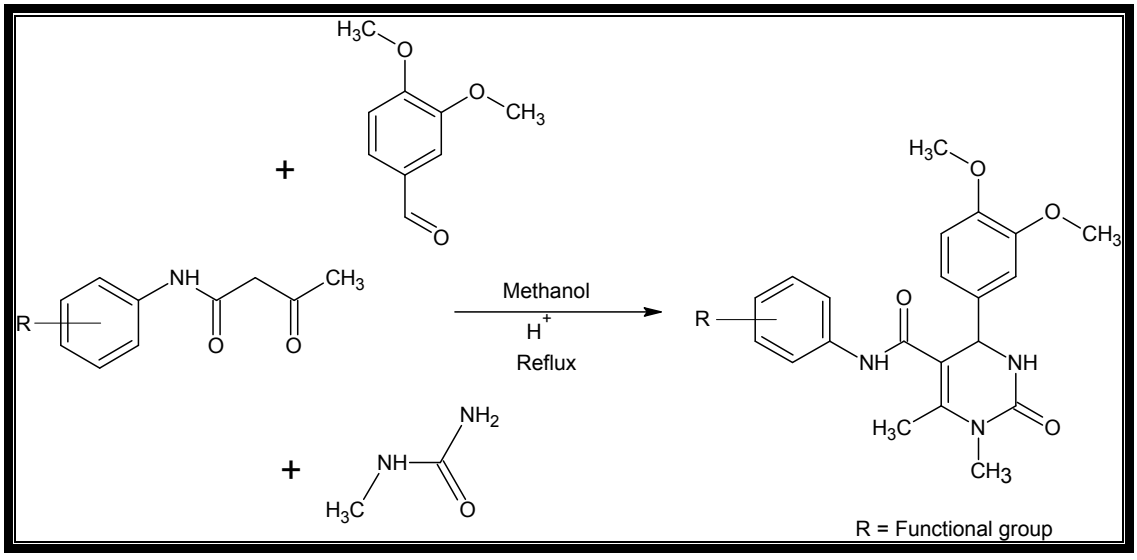


Table 2.3.1: Physical constants of N-methyl pyrimidenes.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. °C	Yield %
1	**RDV-1**	4-OCH_3	$C_{22}H_{25}N_3O_5$	411	0.68	254	52
2	**RDV-2**	4-CH_3	$C_{22}H_{25}N_3O_4$	395	0.49	219	61
3	**RDV-3**	4-Cl	$C_{21}H_{22}ClN_3O_4$	415	0.72	264	49
4	**RDV-4**	2- CH_3	$C_{22}H_{25}N_3O_4$	395	0.66	245	72
5	**RDV-5**	3- OCH_3	$C_{22}H_{25}N_3O_5$	411	0.59	261	69
6	**RDV-6**	4-F	$C_{21}H_{22}FN_3O_4$	399	0.51	251	76
7	**RDV-7**	2,5 – di Cl	$C_{21}H_{21}Cl_2N_3O_4$	450	0.76	244	47
8	**RDV-8**	3-Cl	$C_{21}H_{22}ClN_3O_4$	415	0.71	228	66
9	**RDV-9**	3,4 – di Cl	$C_{21}H_{21}Cl_2N_3O_4$	450	0.54	247	61
10	**RDV-10**	3-Cl, 4-F	$C_{22}H_{25}ClFN_3O_4$	449	0.62	256	65

* Chloroform : Methanol: 9:1

The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized N-methylpyrimidine derivatives are given in Table 2.3.1. The characterization was done by IR, ^{1}H NMR and mass spectra.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 Spectrophotometer in the frequency range of 4000-400 cm^{-}1 by KBr powder method. Figure 2.3.1 shows IR spectra of RDV-1. The IR spectral data for RDV-1 is given in Table 2.3.2. The spectral data for all other compounds are reported in Table 2.3.3.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2.3.2 shows NMR spectra of RDV-1. The spectral data for RDV-1 is given in Table 2.3.4.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 2.3.3 shows mass spectra of RDV-1.The proposed mass fragmentation of the same compound is also given in Scheme 2.3.1.

Figure 2.3.1: IR spectra of 6-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RDV-1)

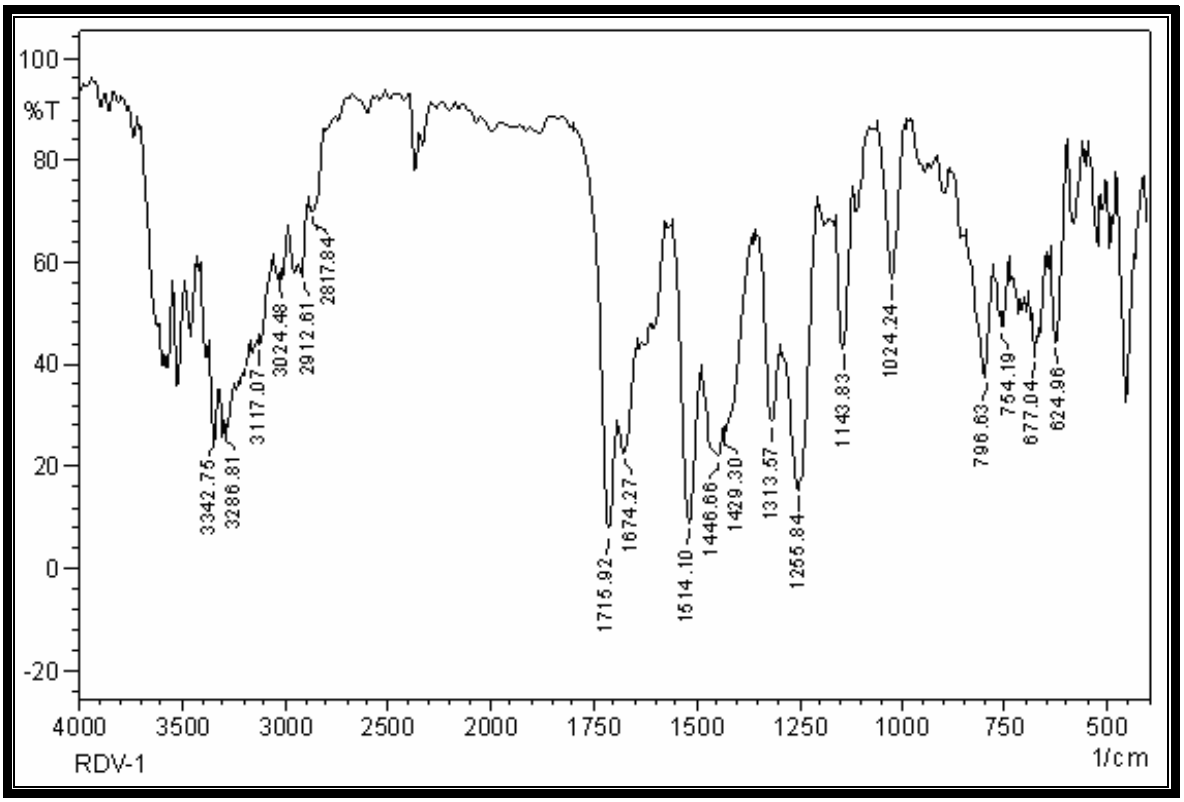


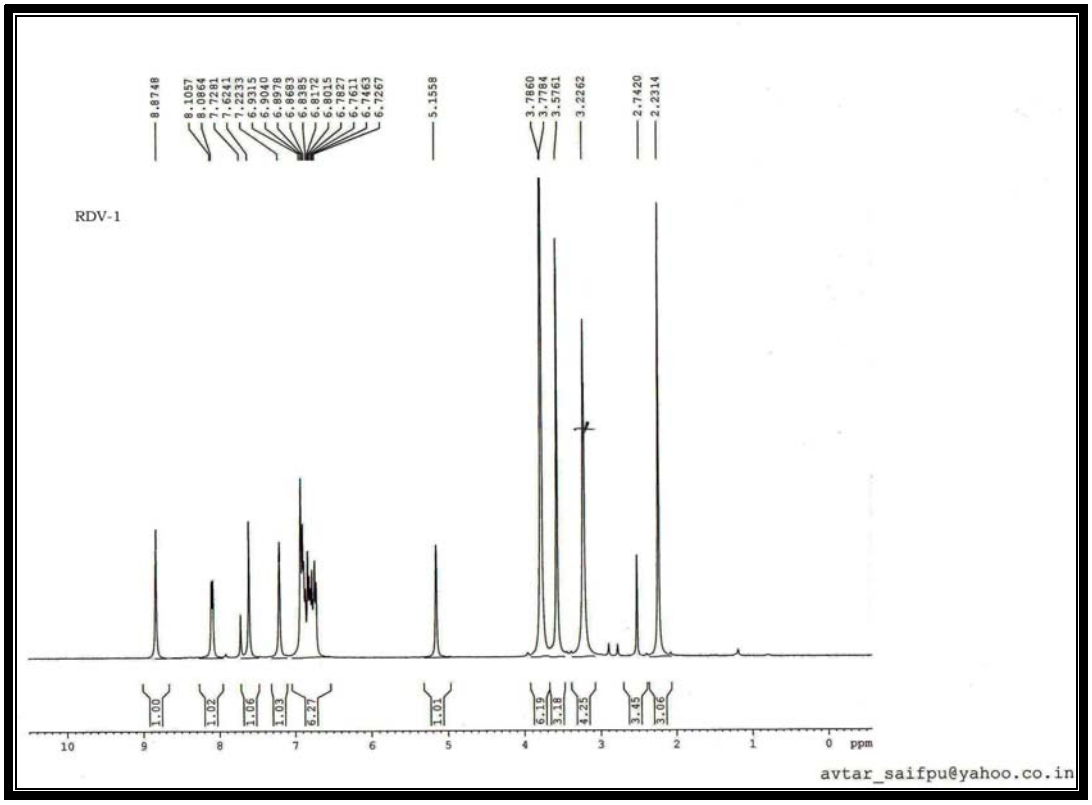
Table 2.3.2: IR spectral data of 6-(3,4-dimethoxyphenyl)-N-(4-methoxy phenyl)-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RDV-1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported
Alkane	C-H str. (asym.)	2912.61	2975-2900
	C-H str. (sym.)	2817.84	2880-2810
	C-H def. (asym.)	1446.66	1480-1435
	C-H def. (sym.)	1313.57	1985-1350
Aromatic	C-H str.	3024.48	3100-3000
	C=C str.	1514.10	1585-1480
	C-H i.p. def.	1143.83	1125-1090
	C-H o.o.p. def.	796.63	860-810
Ketones	C=O str.(cyclic)	1715.92	1740-1680
	C=O str. (aliphatic)	1674.27	1710-1650
Nitrogen	C-N str.	1255.84	1350-1200
	N-H str.	3342.75	3400-3200
	N-H def.	1514.10	1650-1500
Ether	C-O-C str. (asym.)	1143.83	1400-1000
	C-O-C str. (sym.)	1024.24	1075-1020

Table 2.3.3: IR spectral data of synthesized N-methylpyrimidines.

Compounds	*IR ν, (cm^{-1})*					
	C=O (cyclic)	**C=O (alip.)**	**N-H (Str.)**	**C=C (Str.)**	**C-H (asym.)**	**R**
RDV-2	1716.41	1659.20	3289.33	1524.23	2931.63	2835.47
RDV-3	1710.57	1657.90	3257.32	1541.49	2984.20	757.49
RDV-4	1711.12	1683.60	3238.29	1524.53	2944.29	2826.24
RDV-5	1707.23	1668.05	3354.62	1511.17	2928.49	1133.24
RDV-6	1707.54	1679.01	3359.54	1539.51	2956.52	688.11
RDV-7	1716.68	1682.55	3275.61	1542.20	2929.49	756.29
RDV-8	1706.10	1667.47	3361.12	1529.28	2937.40	771.57
RDV-9	1715.37	1666.61	3281.19	1528.24	2961.19	749.24
RDV-10	1709.58	1658.08	3266.08	1540.47	2983.24	676.17

Figure 2.3.2: ^{1}H NMR spectra of 6-(3,4-dimethoxyphenyl)-N-(4-methoxy phenyl)-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RDV-1).



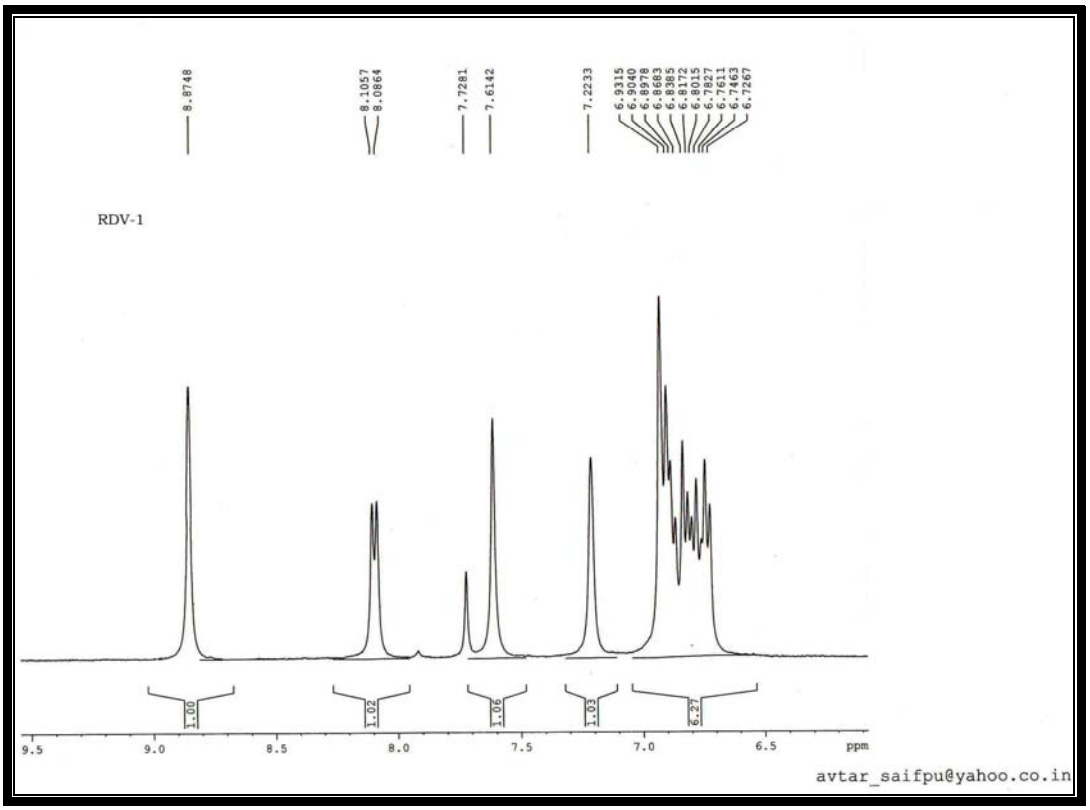
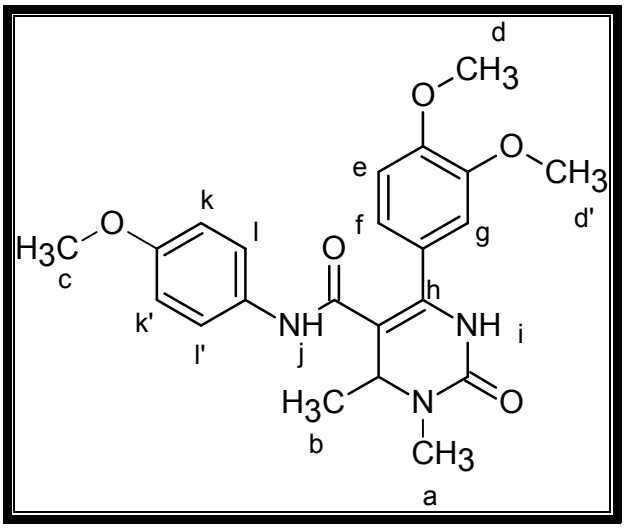
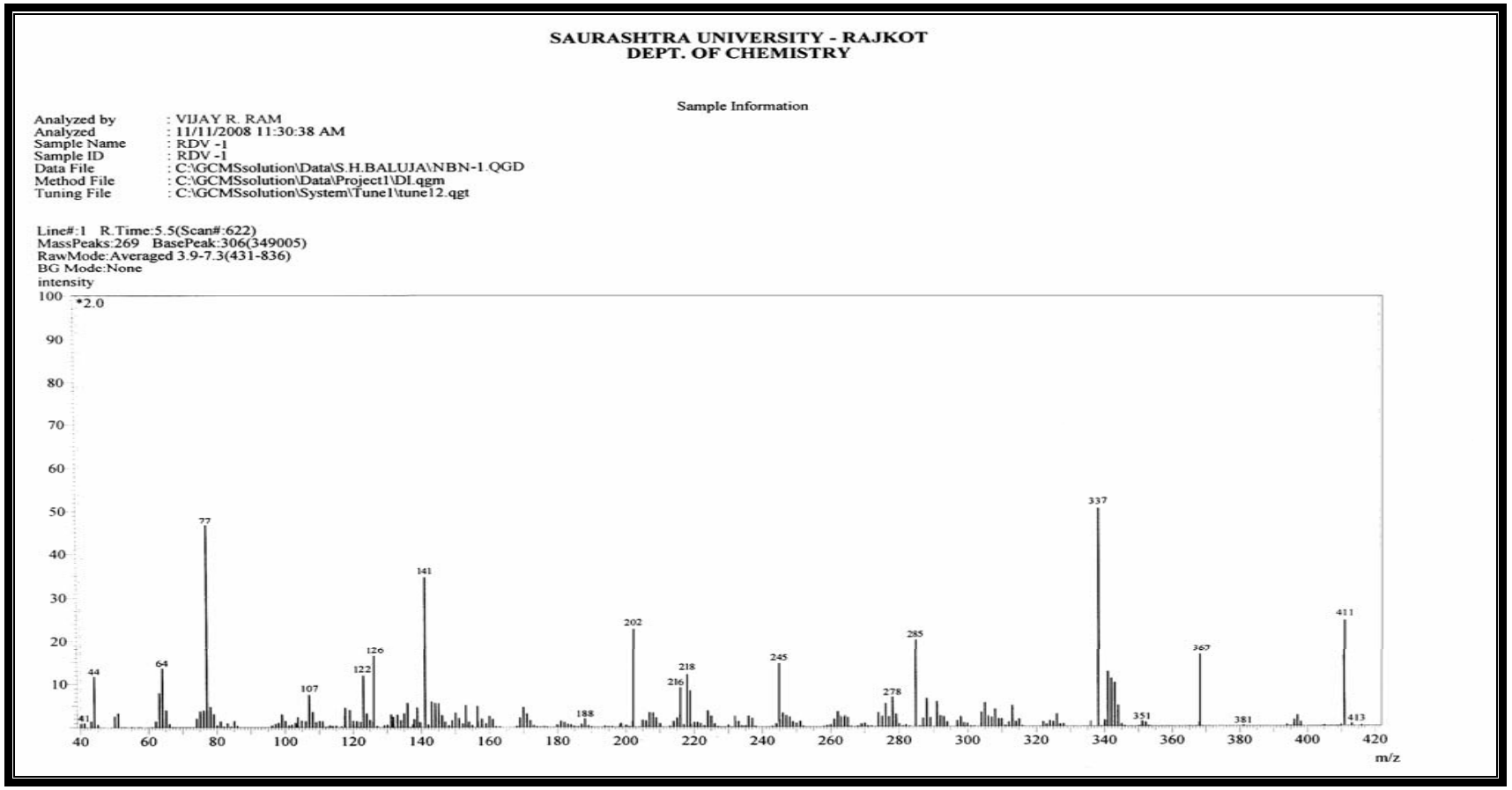


Table 2.3.4: ^{1}H NMR spectral data of 6-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (RDV-1).

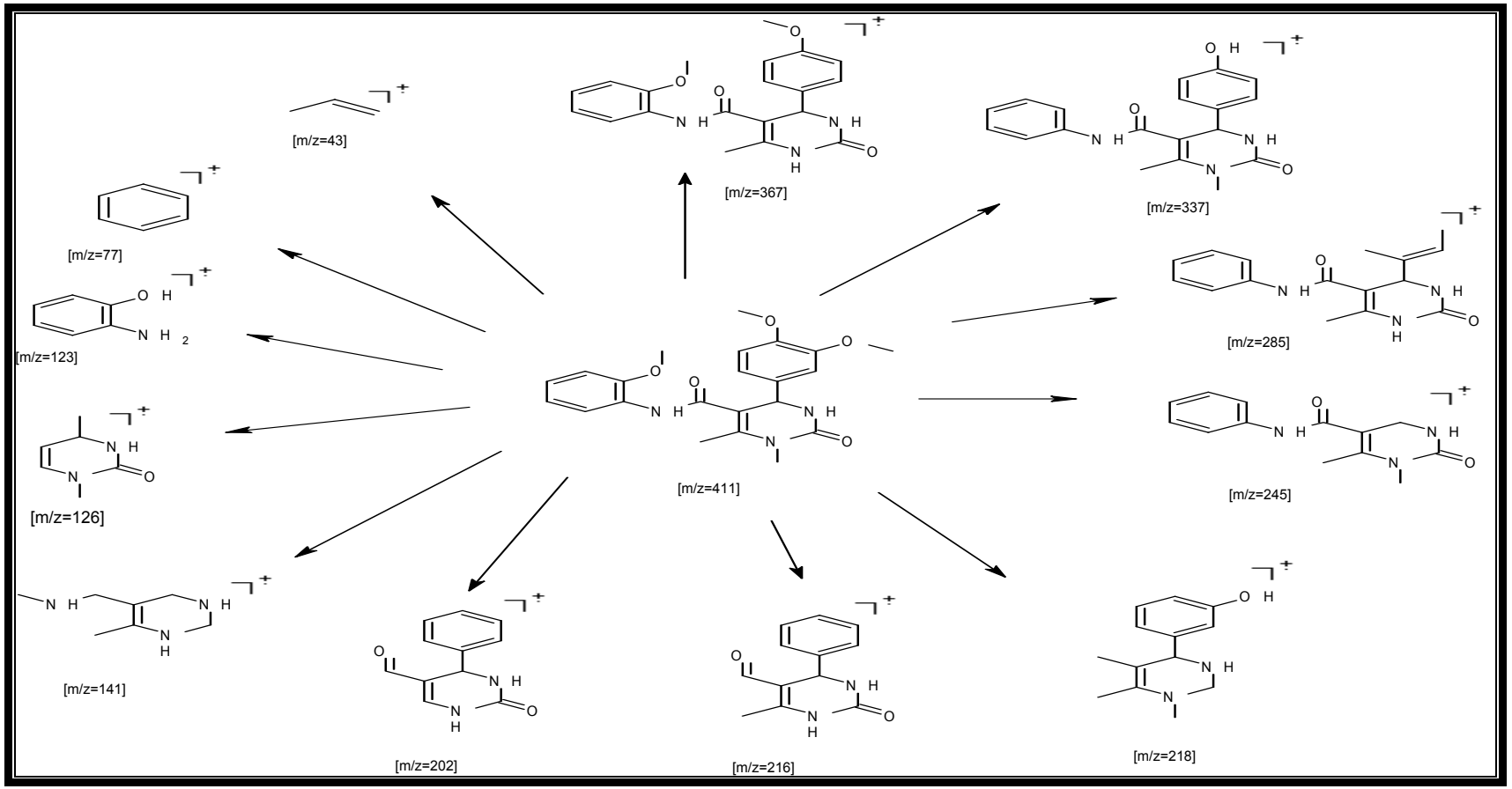


Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	2.24	3H	singlet	-C$\underline{H}_a$	-
2	2.76	3H	singlet	-C$\underline{H}_b$	-
3	3.58	3H	triplet	-OC$\underline{H}_c$	-
4	3.79	6H	singlet	-OC$\underline{H}_{dd'}$	-
5	5.15	1H	singlet	-H_h	-
6	6.46-7.72	7H	multiplat	-Ar-$H_{e\text{-}g,kk'\ ll'}$	-
7	8.10	1H	singlet	-N$\underline{H}_i$	-
8	8.87	1H	singlet	-NH_j	-

Figure 2.3.3: Mass spectra of 6-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (RDV-1).



Scheme 2.3.1: Proposed mass fragmentation of 6-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-3,4-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RDV-1).



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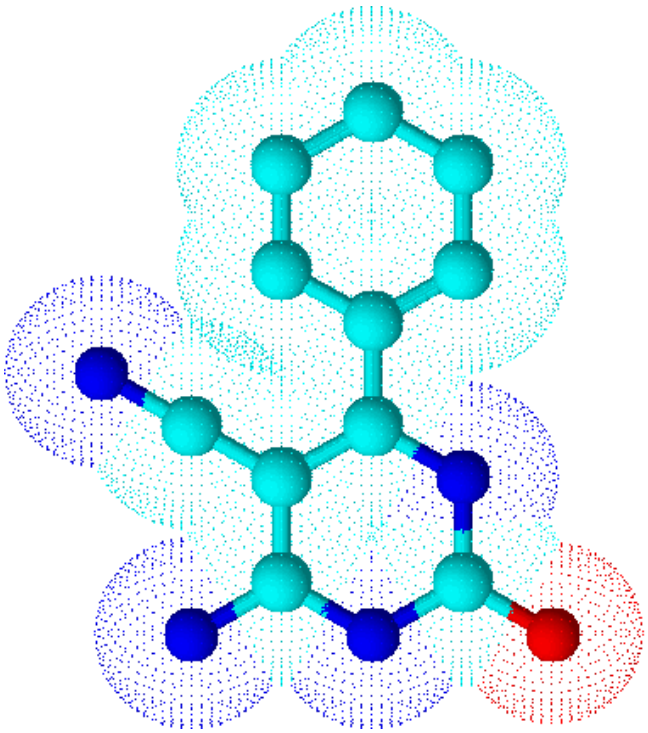


Section-IV

Synthesis of Tetrahydropyrimidines

INTRODUCTION

The chemistry and the synthesis of tetrahydropyrimidine have been attracting widespread attention in recent years. The present popularity of these compounds is mainly due to their close structural relationship to the clinically important dihydropyridine calcium channel blockers[1–6].

Literature survey shows that lots of work has been done for tetrahydropyrimidines. Many researchers have been worked on QSAR study of tetrahydropyrimidines[7-9]. Zhang and co-workers have reported the synthesis of tetrahydropyrimidine via catalyst free multicocmponent reaction[10]. One pot synthesis of these compounds has been reported by Akbar et al.[11] using zeolite as catalyst. Perumal and co-workers[12] have synthesized tetrahydropyrimidines using phosphotungstic acid. Using microwave irradiation, Roy and Bordoloi[13] have synthesized some new tetrahydropyrimidines. Zhao and Liu[14] have reported the synthesis of novel fluoroalkylated multifunctional tetra hydropyrimidines. The stereomutations of conformational atropisomers of hindered 1,2-diaryltetrahydropyrimidines has been reported by Gracia and co-worker[15]. Baldev et al[16] have reported the thermal and microwave assisted synthesis of tetrahydropyrimidines. By ultrasonic irradiation, Muravyova[17] et al have synthesized some new tetrahydropyrimidines.

Tetrahydropyrimidine is known as a versatile heterocyclic compound which has been subjected to a large variety of structural modifications in order to synthesize derivatives with different biological properties. Their various condensed derivatives are reported to possess calcium antagonist,[18–20] anti-inflammatory,[21–23] analgesic,[24] antitumor,[25, 26] antidepressant,[27] antibacterial, and antifungal effects.[28–30] Several synthetic approaches have been reported for the synthesis of fused heterocyclic pyrimidine derivatives.[31–33] These compounds act as muscarinic agonist in the rat central nervous system.[34, 35] William and co-workers have reported the M1 receptor of tetrahydropyrimidines and their biochemical activity.[36] The antidepressant[37] and fungicidal[38] activity of some of these derivatives have also been reported. Upshall[39] has reported the nicotinic activity whereas Faust and co-workers[41] have reported the antihypertensive activity of these compounds.

Thus, due to the importance of biological active tetrahydropyrimidines, the present chapter describes the synthesis and characterization of some tetrahydropyrimidine derivatives.

EXPERIMENTAL

Synthesis of 4-amino-2-hydroxy-6-phenyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile:

A mixture of substituted aldehyde (0.01 M), malenonitrile (0.01 M) and urea (0.012 M) in methanol was refluxed for 5 hours. The product was isolated and crystallized from ethanol. All the synthesized compounds were recrystallized from ethanol.

REACTION SCHEME

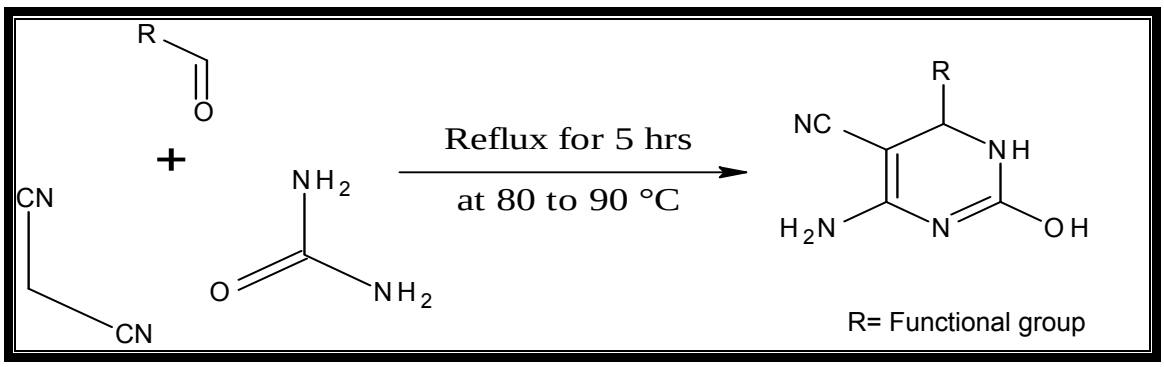


Table 2.4.1: Physical constants of Tetrahydropyrimidenes.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. ^oC	Yield %
1	**SAR-1**	$-C_6H_5$	$C_{11}H_{12}N_4O$	216	0.52	64	93
2	**SAR-2**	$4\text{-Cl-}C_6H_4$	$C_{13}H_{13}ClN_4O$	250	0.61	110	80
3	**SAR-3**	Cinnamaldehyde	$C_{13}H_{14}N_4O$	242	0.66	146	94
4	**SRA-4**	$3\text{-Cl-}C_6H_4$	$C_{13}H_{13}ClN_4O$	250	0.49	150	70
5	**SAR-5**	$4\text{-F-}C_6H_4$	$C_{11}H_{11}FN_4O$	234	0.58	134	59
6	**SAR-6**	$4\text{-}OCH_3\text{-}C_6H_4$	$C_{12}H_{14}N_4O_2$	246	0.49	154	60
7	**SAR-7**	$3\text{-}NO_2\text{-}C_6H_4$	$C_{11}H_{11}N_5O_3$	261	0.71	184	77
8	**SAR-8**	Vaniline	$C_{12}H_{14}N_4O_3$	262	0.57	115	50
9	**SAR-9**	Furfuraldehyde	$C_9H_{10}N_4O_2$	206	0.50	80	76
10	**SAR-10**	$4\text{-OH-}C_6H_4$	$C_{11}H_{12}N_4O_2$	232	0.48	70	85

* Chloroform:Methanol:- 9:1

The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized tetrahydropyrimidine derivatives are given in Table 2.4.1.The characterization was done by IR, ^{1}H NMR and mass spectra.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 Spectrophotometer in the frequency range of 4000-400 cm^{-1} by KBr powder method. Figure 2.4.1 shows IR spectra of SAR-2. The IR spectral data for SAR-2 is given in Table 2.4.2. The spectral data for all other compounds are reported in Table 2.4.3.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2.4.2 shows NMR spectra of SAR-2. The spectral data for SAR-2 is given in Table 2.4.4.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 2.4.3 shows mass spectra of SAR-2.The proposed mass fragmentation of the same compound is also given in Scheme 2.4.1.

Figure 2.4.1: IR spectra of 4-amino-6-(4-chlorophenyl)-2-hydroxy-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (SAR-2).

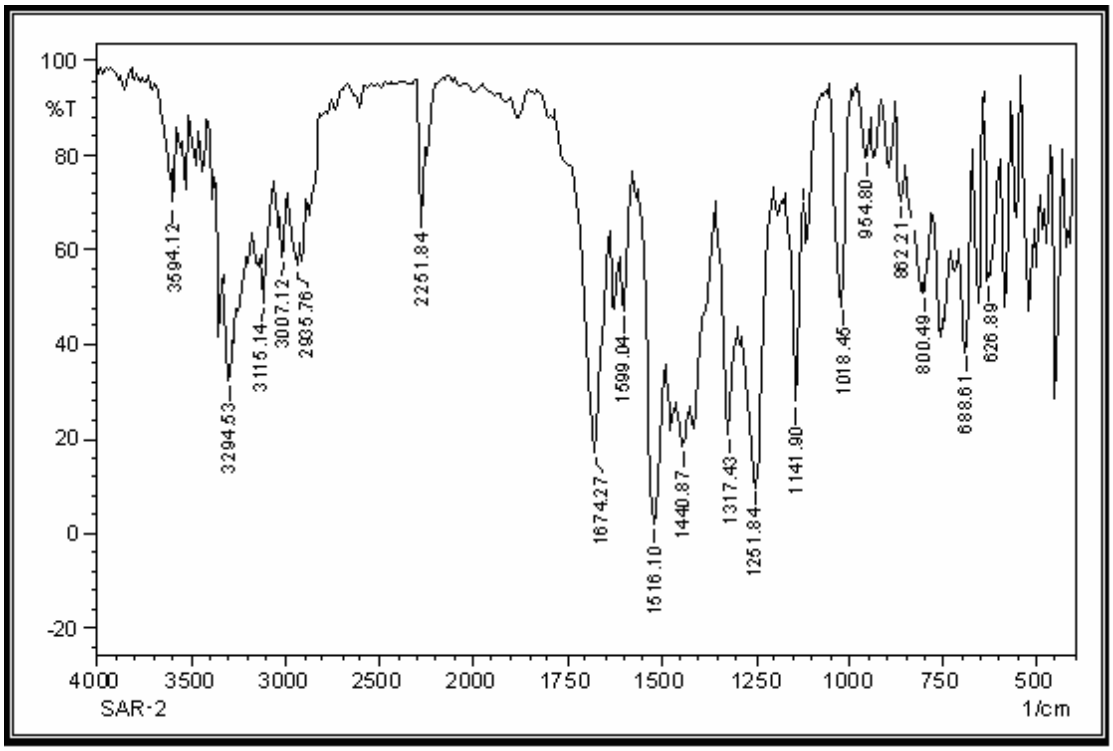


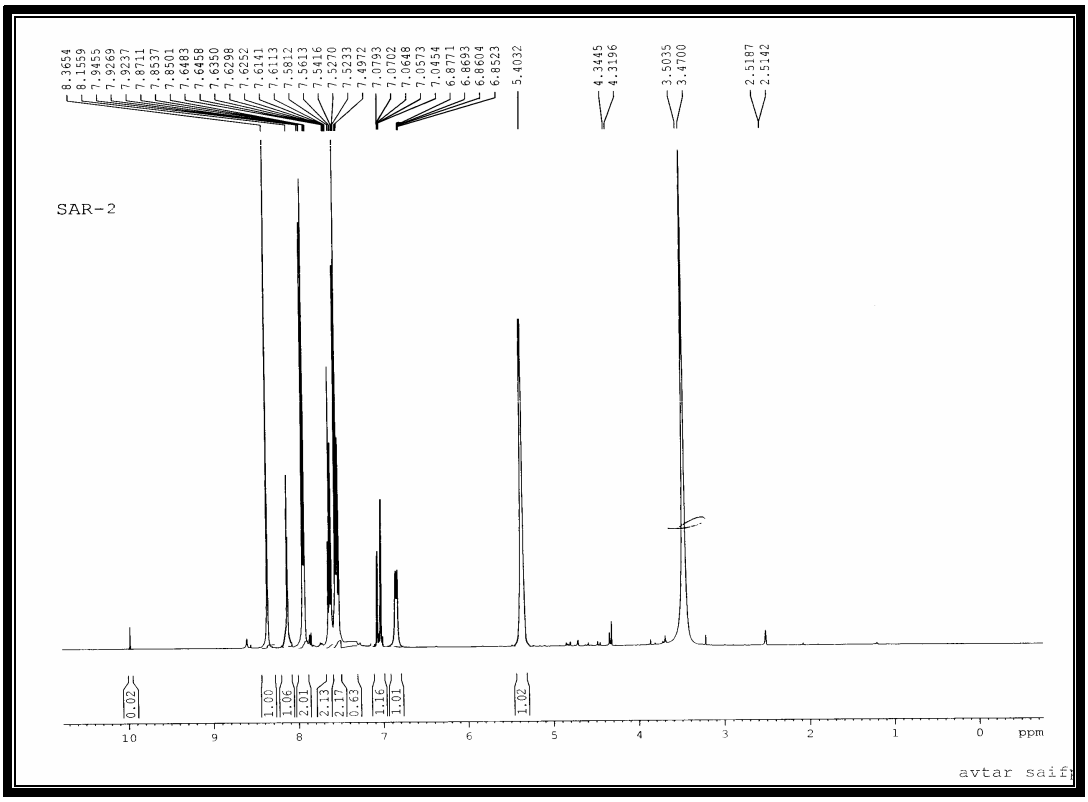
Table 2.4.2: IR spectral data of 4-amino-6-(4-chlorophenyl)-2-hydroxy-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (SAR-2).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported
Alkane	C-H str. (asym.)	2935.76	2975-2900
	C-H str. (sym.)	2867	2880-2810
	C-H def. (asym.)	1440.87	1480-1435
	C-H def. (sym.)	1351	1985-1350
Aromatic	C-H str.	3007.12	3100-3000
	C=C	1516.10	1585-1480
	C-H i.p. def.	1141.90	1125-1090
	C-H o.o.p. def.	862.21	860-810
Nitrile	C≡N str.	2251.84	2210-2280
Alcohol	O-H str.	3594.12	3600-3450
Nitrogen	C-N str.	1317.43	1350-1200
	N-H str.	3294.53	3400-3200
	N-H def.	1599.04	1650-1500
Ether	C-O-C str. (asym.)	1141.90	1400-1000
	C-O-C str. (sym.)	1018.45	1075-1020

Table 1.3: IR spectral data of synthesized Tetrahydropyrimidenes.

Compounds	*IR ν, (cm^{-1})*					
	O−H (Str.)	**N−H (Str.)**	**C≡N (str.)**	**C=N (Str.)**	**C−H (asym.)**	**R**
SAR-1	3524.12	3389.12	2235.12	1684.21	2933.45	-
SAR-3	3499.41	3412.27	2214.32	1654.87	2912.37	786
SAR-4	3529.22	3437.54	2241.51	1627.31	2962.21	1543.34
SAR-5	3535.47	3388.12	2220.54	1629.14	2945.39	746.34
SAR-6	3564.10	3356.21	2268.34	1647.61	2941.24	651.27
SAR-7	3584.32	3377.54	2245.76	1630.24	2954.67	1139.33
SAR-8	3568.22	3364.30	2278.94	1655.84	2920.20	681.28
SAR-9	3486.24	3394.61	2218.58	1634.67	2961.84	-
SAR-10	3530.65	3408.27	2282.54	1672.29	2933.48	3527.99

Figure 2.4.2: ^{1}H NMR spectra of 4-amino-6-(4-chlorophenyl)-2-hydroxy-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (SAR-2).



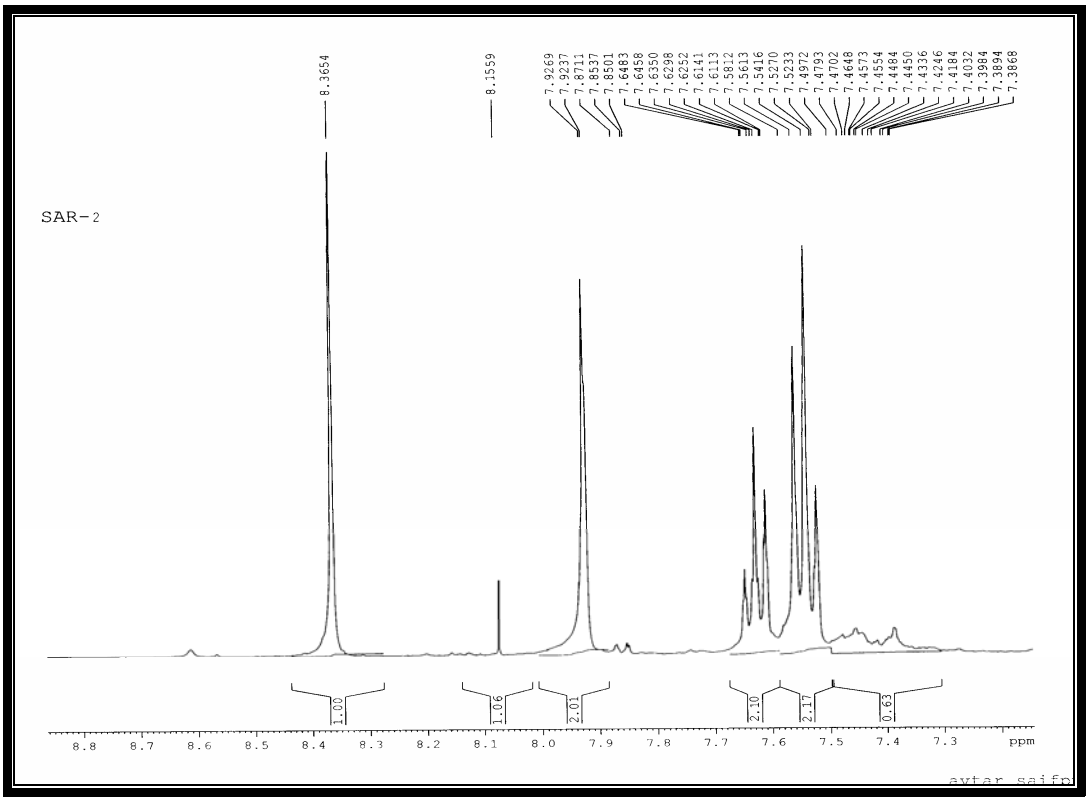
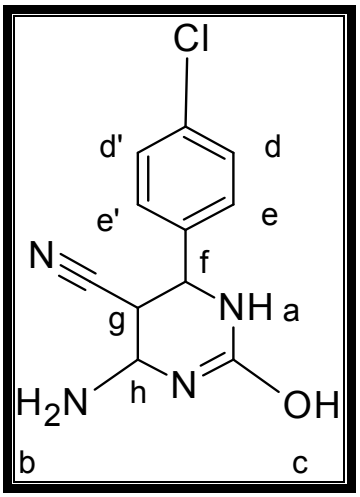
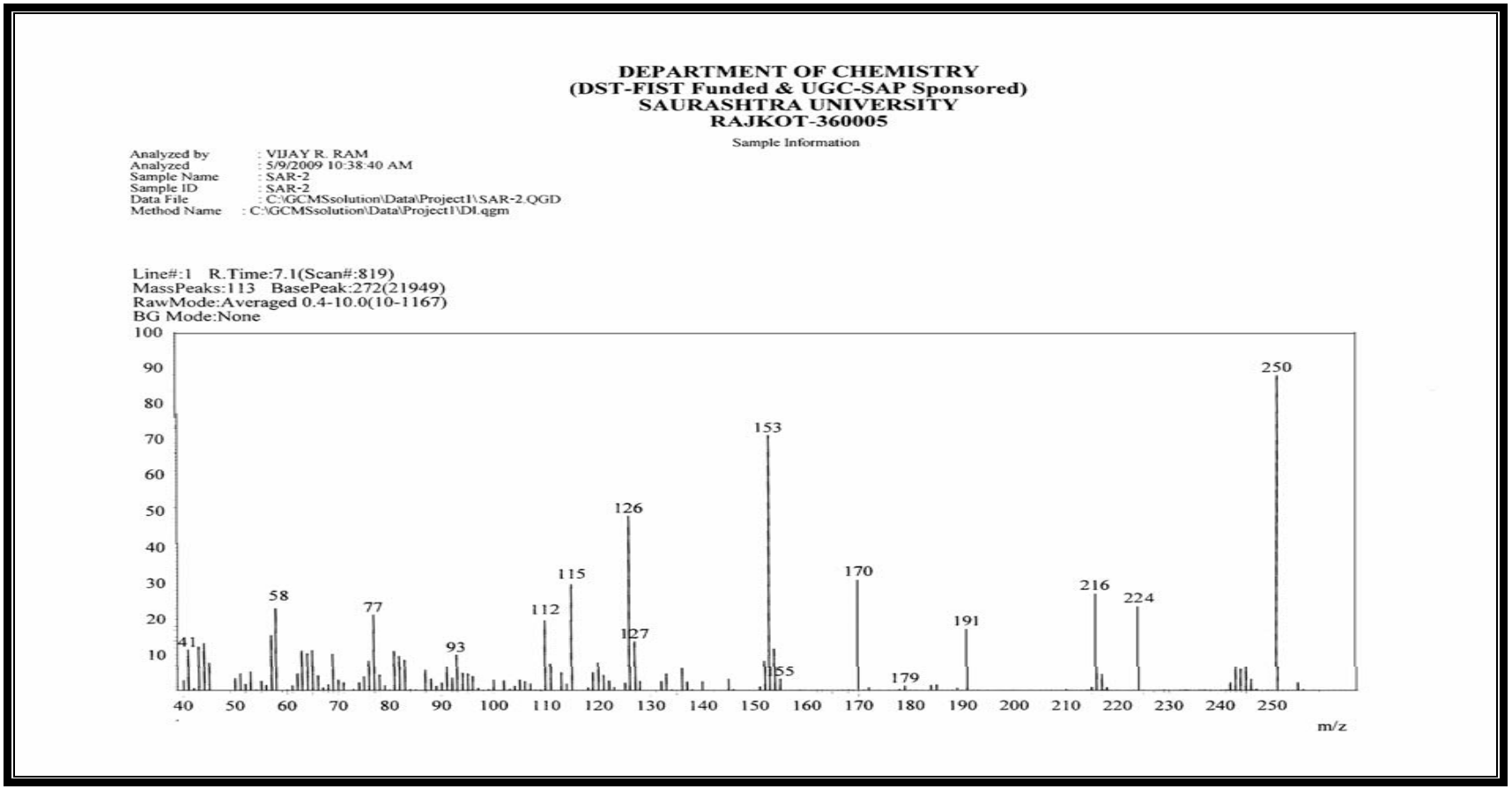


Table 2.4.4: ^{1}H NMR spectral data of 4-amino-6-(4-chlorophenyl)-2-hydroxy-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (SAR-2).

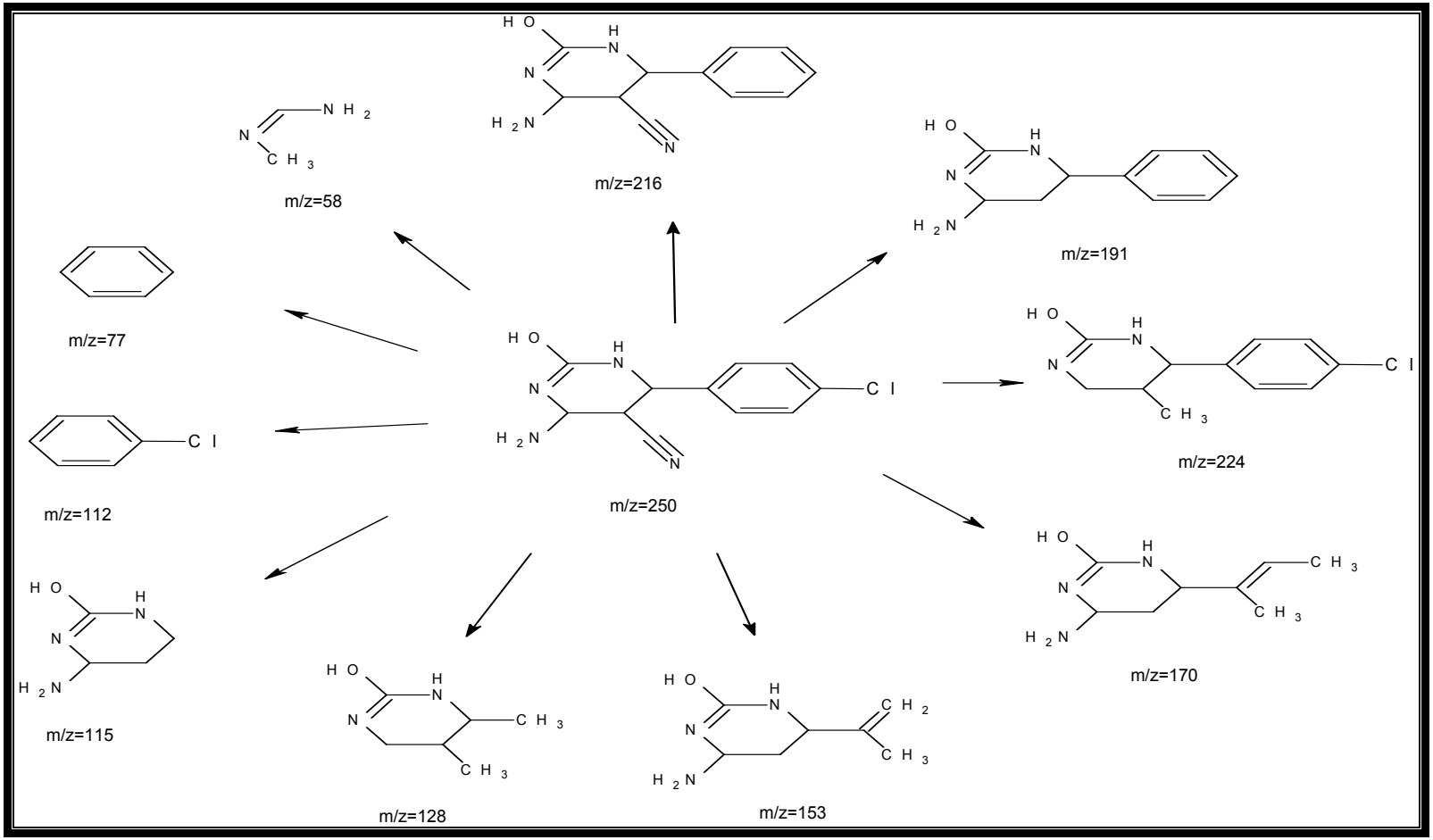


Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	8.15	1H	singlet	-N<u>H</u>$_a$	-
2	7.87-7.94	2H	singlet	-N<u>H</u>$_b$	-
3	8.36	1H	singlet	-O<u>H</u>$_c$	-
4	6.85-6.87	2H	doublet	-Ar-<u>H</u>$_{dd'}$	6.80
5	7.04-7.07	2H	doublet	-Ar-H$_{ee''}$	5.16
7	5.40	1H	singlet	-Ar-H$_f$	-
8	7.45-7.64	2H	singlet	-Ar-H$_{g,h}$	-

Figure 2.4.3: Mass spectra of 4-amino-6-(4-chlorophenyl)-2-hydroxy-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (SAR-2).



Scheme 2.4.1: Proposed mass fragmentation of 4-amino-6-(4-chlorophenyl)-2-hydroxy-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (SAR-2).



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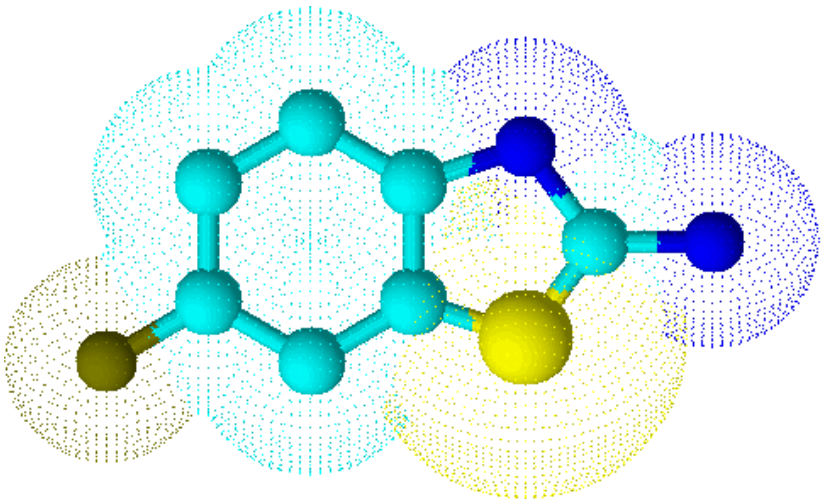
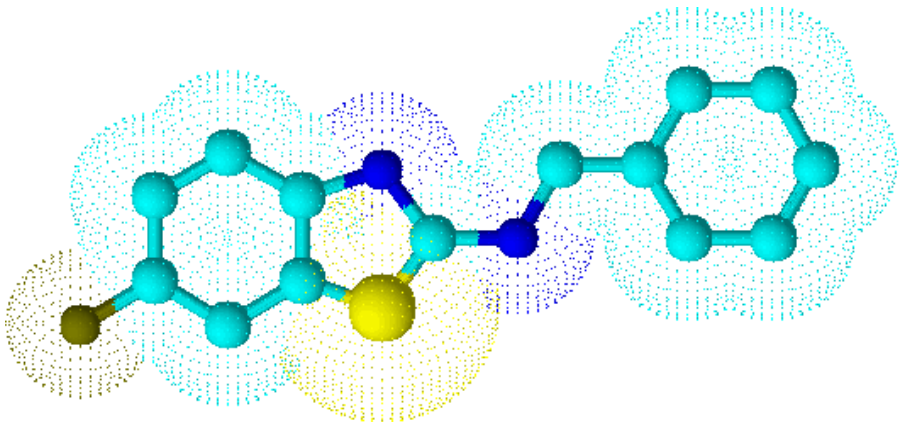


Part-2

Synthesis of Benzothiazole Derivatives



Synthesis of Azomethines

INTRODUCTION

Benzothiazole derivatives are of particular interest within the realm of medicinal chemistry[1]. Pyrazole ring system is of some practical importance, because many drugs and medicines contain a pyrazole ring system. As early as 1884 Knorr discovered the antipyretic (temperature reducing) action of a pyrazole derivative in human beings and due to its antipyretic property, he named the compound “Antipyrine”.

Biologistis attention was drawn to this class of series when the pharmacological profile of Riluzole was discovered. Thereafter, benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity. These compounds possess selective analgesic[2], antiinflammatory[3], antitumer[4], antitubercular[5], anticonvulsant[6], diuretic[7] and antimicrobial[8] etc., properties.

It is well known that the introduction of fluorine atom into an organic molecule causes dramatic changes in its biological profile, mainly due to high electronegativity of fluorine, the strong carbon-fluorine bond and increased solubility in lipids[9]. In search for new biodynamic potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in the β-lactam nucleus and study their biological and pharmacological activity[10]. The literature survey prompted us to synthesize some new substituted fluoro benzothiazole, azomethines as target compounds.

The chemistry of the carbon-nitrogen double bond plays a vital role in the progress of chemistry science[11]. azomethines compounds have been used as fine chemicals and medical substrates. azomethines are important class of ligands due to their synthetic flexibility, their selectivity and sensitivity towards the central metal atom, structural similarities with natural biological substances and also due to presence of imine group (N=CH-) which imports in elucidating the mechanism of transformation and rasemination reaction in biological system[12-14]. They are well known intermediates for the preparation of azetidinone, thiazolidinone, formazone, arylacetamide and many other derivatives. The transformation of azomethines in the secondary amines via reduction[15] or Grignard reagents addition[16] or the cycloaddition of these azomethines[17], is well known but a series of less investigated reactions, such

as conversion to amides after the treatment with tri alkyl boranes and CO in the presence of cobalt carbonyl[18], Darzens-type condensations[19] or Wittig reaction with phosphorus ylides[20] have also been reported.

Azomethines has a wide range of applications such as corrosion inhibitor[21], intermediates in various reactions[22, 23], in perfumery[24] etc. Some are known to be used in many potential drugs[25] and are known to posses broad spectrum of biological activities such as antiviral[26], anticancer[27], anti HIV[28, 29], antifungal[30], antiparasitic[31], anti-inflammatory[32], anticonvulsant[33], antitumor[34, 35], antioxidant[36], antiulcerogenic[37] etc. The antitubercular[38] or cytostatic[39] activity of azomethines has been known for long and a large number of azomethines have been tested as non terpenoid insectjuvenile hormone mimics[40].

Synthesis of azomethines is often carried out with acid-catalyzed and generally by refluxing the mixture of aldehyde (or ketone) and amine in organic medium[41]. However, with the assistance of microwave irradiation, it was found that the condensation reaction of salicylaldehyde and various aryl amines could proceed fast and efficiently without solvent. Sun et al[42] have reported the rapid synthesis of azomethines without solvent under microwave irradiation. Desai and Mistry[43] have reported the microwave synthesis and biological evaluation of some azomethines. Various workers reported the synthesis of azomethines by ultrasound irradiation[44-47].

Literature survey shows that a lot of work has been done related to azomethines and their metal complexes. Corbin and work[48] have reported the azomethines-zinc complex from benzthiazolines. Hamil and co-workers[49] have reported the cobalt and copper complexes of azomethines and their antibacterial studies. Rajavel and Krishnan[50] have reported the synthesis and characterization of oxovanadium(IV) complexes of the azomethines derived by the condensation of 2-aminobenzaldehyde with various diamines as 1,2-diaminoethane, 1,2-diaminopropane, 1,3-diaminopropane.

In recent years, a lot of work has been done by various workers to synthesize azomethines and further thiazolidinones, azetidinones etc from benzothiazole nucleus. Pai and Chavan[51] have reported the synthesis and antibacterial activity of azetidinones via azomethines from benzothiazole moiety. Vijaykumar and co-workers[52] have synthesized the azetidinones via

azomethines from thiazole nucleus. Synthesis and antimicrobial activity of crown ethers of azomethines type have also reported[53]. Sie-tiong et al.[54] have reported the mesogenic properties of azomethines comprising benzothiazole moiety. Zahid and Claudiu[55] have also reported the antibacterial activity of copper and nickel complexes of benzothiazole derived azomethines.

Thus, with an effort to capitalize the biological potential of the heterocyclic system and to provide more interesting compounds for biological study, the present work undertaken to synthesize some azomethines bearing benzothiazole nucleus.

EXPERIMENTAL

Synthesis of 6-fluoro-N-[(Z)-phenylmethylidene]-1, 3-benzothiazol-2-amine

[A] Synthesis of 6-fluoro-1,3-benzothiazol-2-amine:

To a solution of p-flouro aniline (1 mole) in chlorobenzene, concentrated sulfuric acid (0.55 mole) was added drop wise over a period of 5 minutes. To this finely divided suspension of p-fluoro aniline sulfate, sodium thiocyanate (1.1 mole) was added and the mixture was heated for 3 hours at 100° (inside temperature) in an oil bath. The solution, which now contains the thiourea, was cooled to 30°C and 1.34 moles of sulfuryl chloride was added over a period of 15 minutes, with care that the temperature does not exceed 50°C. The mixture was kept at 50°C for 2 hours (no further evolution of hydrogen chloride) and then the chlorobenzene is removed by filtration. The solid residue was then dissolved in hot water. It was further washed by a current of steam to remove remaining solvent. The resulting solid was re precipitated from alkaline solution. For this, the solid residue was dissolved in concentrated ammonium hydroxide (sp. gr. 0.90). To this alkaline solution, HCl (o.1 N) was added drop wise and stirred. The 6-fluoro-1,3-benzothiazol-2-amine is precipitated, filtered and washed with water. The crude product was isolated and crystallized from absolute ethanol.

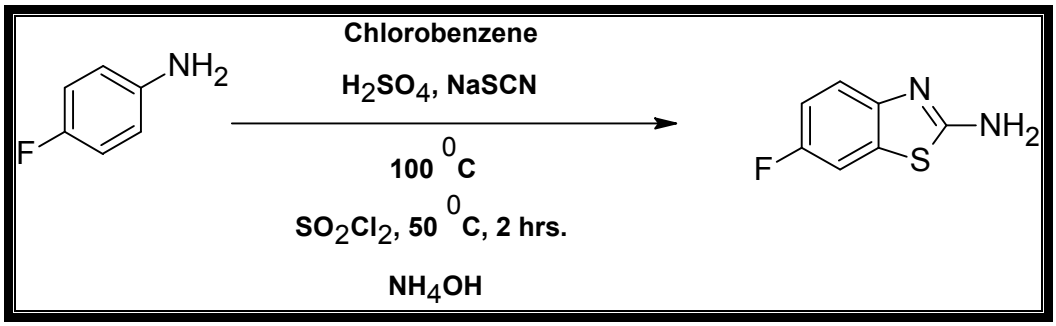
[B] Synthesis of 6-fluoro-N-[(E)-(4-methylphenyl)methylidene]-2,3-dihydro-1,3-benzothiazol-2-amine:

An ethanolic solution of 6-flouro 2-amino benzothiazole (0.01 M), 4-methyl benzaldehyde (0.01 M) and glacial acetic acid (as catalyst) was refluxed for 10 hrs. The reaction was monitoring with TLC. The product was isolated and crystallized from absolute ethanol.

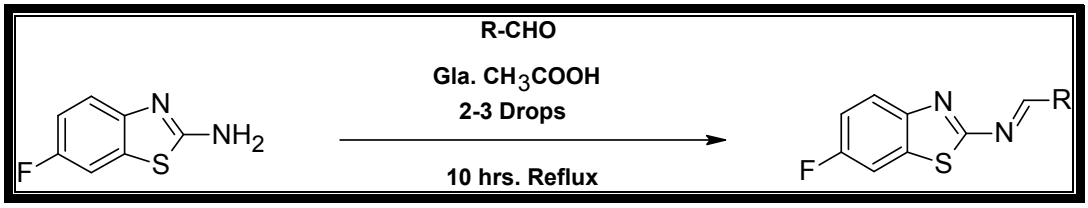
Similarly, other azomethines were synthesized.

REACTION SCHEME

[A] Synthesis of 6-methoxy 2-amino benzothiazole:



[B] 6-fluoro-N-[(E)-(4-methylphenyl)methylidene]-2,3-dihydro-1,3-benzothiazol-2-amine:



The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized azomethines are given in Table 2.1.

Table 2.1: Physical constants of synthesized Azomethines.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. °C	Yield %
1	BT-1	4-$N(CH_3)_2$	$C_{16}H_{14}FN_3S$	299	0.59	163	81
2	BT-2	4-CH_3	$C_{15}H_{11}FN_2S$	270	0.62	154	76
3	BT-3	4-Cl	$C_{14}H_8ClFN_2S$	290	0.48	202	58
4	BT-4	3,4 di-OCH_3	$C_{16}H_{13}FN_2O_2S$	316	0.66	176	73
5	BT-5	4-OCH_3	$C_{15}H_{11}FN_2OS$	286	0.46	189	64
6	BT-6	4-F	$C_{14}H_8F_2N_2S$	274	0.75	164	66
7	BT-7	2-OCH_3	$C_{15}H_{11}FN_2OS$	286	0.62	171	49
8	BT-8	3-Cl	$C_{14}H_8ClFN_2S$	290	0.67	213	47
9	BT-9	4-NO_2	$C_{14}H_8FN_3O_2S$	301	0.81	210	41
10	BT-10	2,5-di Cl	$C_{14}H_7Cl_2\ FN_2S$	325	0.73	190	67

* Hexane:Ethyl acetate - 7:3

The characterization was done by IR, ^{1}H NMR and mass spectra.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 Spectrophotometer in the frequency range of 4000-400 cm^{-1} by KBr powder method. Figure 2.1 shows IR spectra of BT-2 whereas its IR spectral data is given in Table 2.2. The spectral data for all other compounds are reported in Table 2.3.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2.2 and Table 1.4 show NMR spectra and spectral data of BT-2.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 2.3 shows mass spectra of BT-2.The proposed mass fragmentation of the same compound is also given in Scheme 2.1.

Figure 2.1: IR spectra of 6-fluoro-N-[(Z)-(4-methylphenyl)methylidene] - 1,3-benzothiazol-2-amine (BT-2).

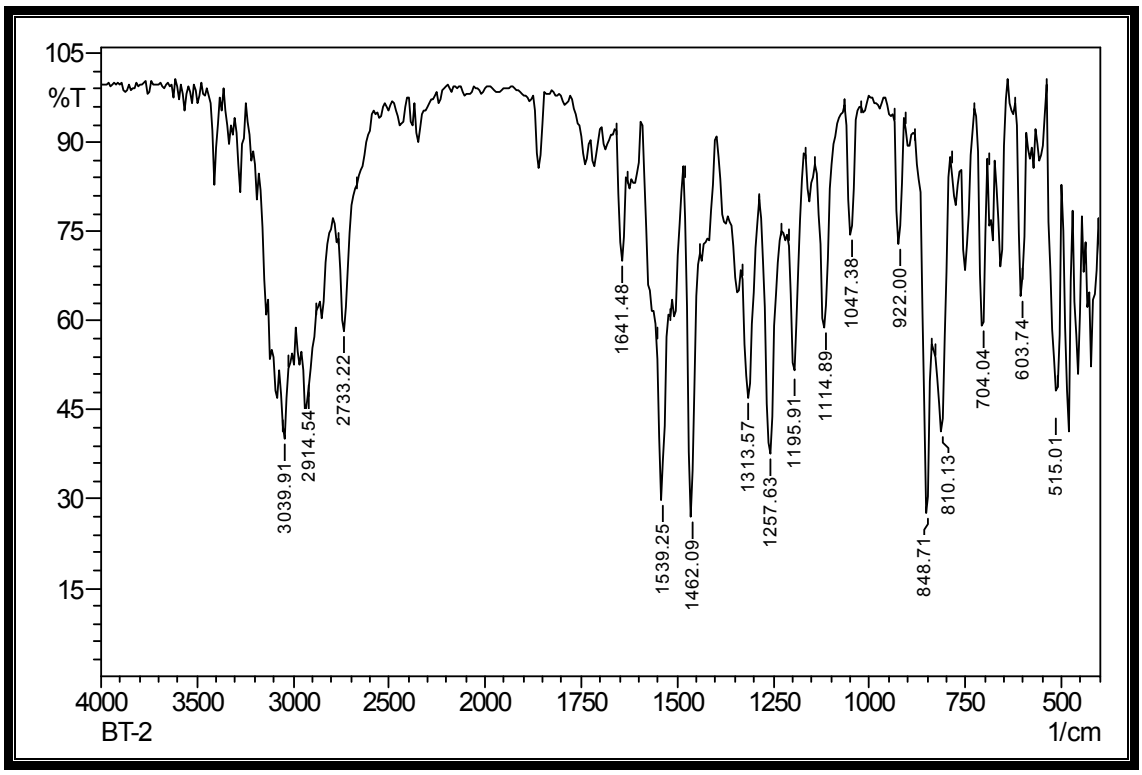


Table 2.2: IR spectral data of 6-fluoro-N-[(Z)-(4-methylphenyl) methylidene]-1,3-benzothiazol-2-amine (BT-2).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported
Alkane	C-H str. (asym.)	2914.54	2975-2900
	C-H str. (sym.)	2843	2880-2810
	C-H def. (asym.)	1462.09	1480-1435
	C-H def. (sym.)	1367	1985-1350
Aromatic	C-H str.	3039.91	3000-3100
	C=C str.	1539.25	1585-1480
	C-H i.p. def.	1147.38	1125-1090
	C-H o.o.p. def.	848.71	860-810
Azomethine	N=C str.	1641.48	1620-1580
	C-N str.	1257.63	1350-1200
Ether	C-O-C str. (asym.)	1195.91	1275-1200
	C-O-C str. (sym.)	1047.38	1075-1020
Halogen	C-F	1114.89	1400-1000

Table 2.3: IR spectral data of synthesized Azomethines.

Compounds	*IR ν, (cm^{-1})*					
	C=N (Str.)	**C-N (Str.)**	**C-F (Bend.)**	**C=C (Str.)**	**C-H (str. asym.)**	**R**
BT-1	1608.69	1242.20	1145.75	1539.25	2912.61	1242.27
BT-3	1621.27	1247.99	1128.49	1537.34	2933.83	756.21
BT-4	1599.97	1238.34	1145.37	1508.37	2920.32	1165.32
BT-5	1618.33	1257.63	1116.82	1533.46	2922.25	1187.12
BT-6	1608.29	1246.06	1153.47	1545.03	2941.54	1129.17
BT-7	1599.04	1259.56	1112.96	1500.67	2967.23	1177.37
BT-8	1610.31	1242.23	1109.34	1519.96	2971.35	716.24
BT-9	1602.45	1236.54	1137.45	1529.37	2915.64	624.31
BT-10	1600.84	1257.68	1141.90	1536.34	2933.12	784.28

Figure 2.2: ^{1}H NMR spectra of 6-fluoro-N-[(Z)-(4-methylphenyl) methylidene]-1,3-benzothiazol-2-amine (BT-2).

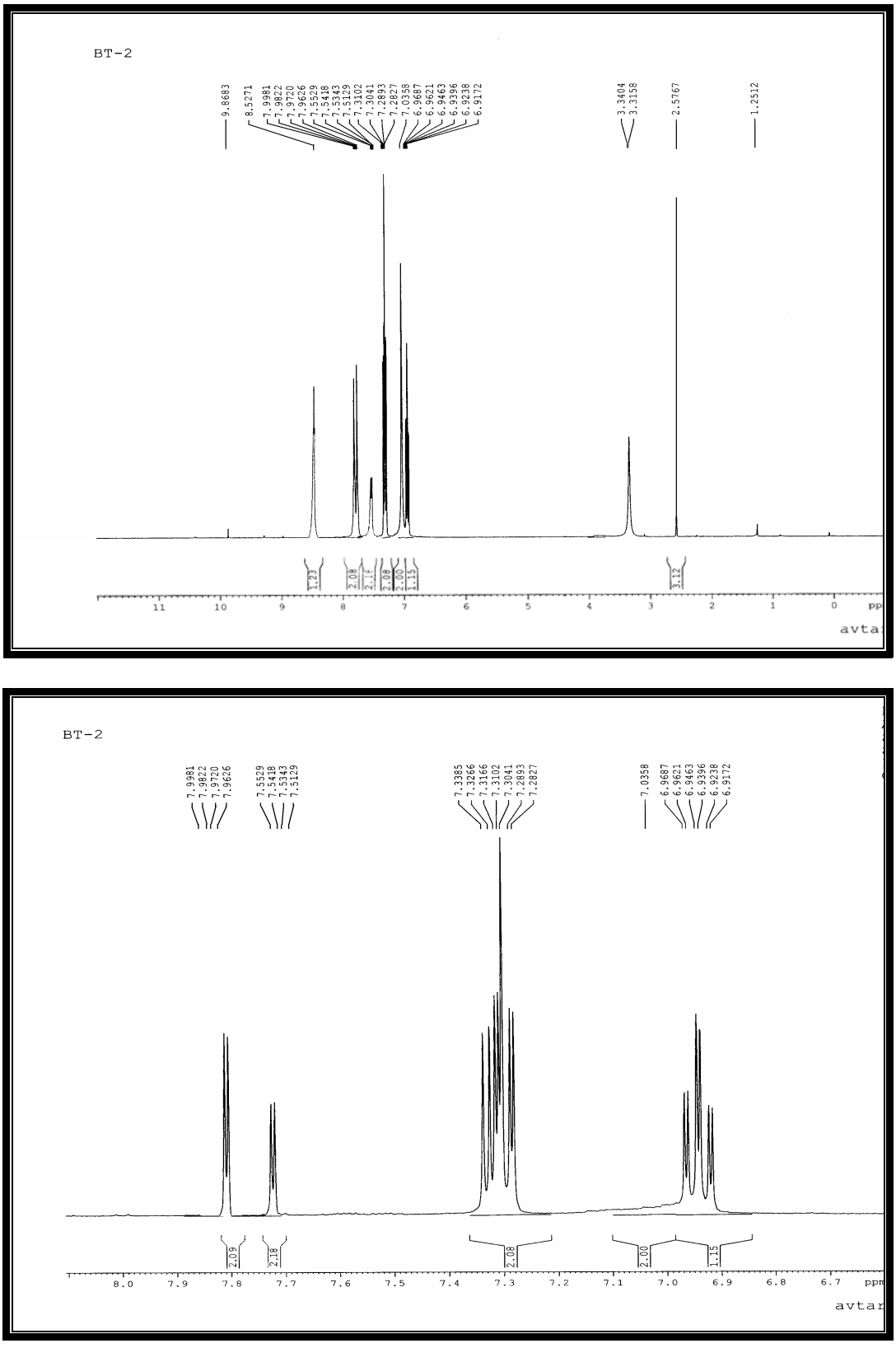
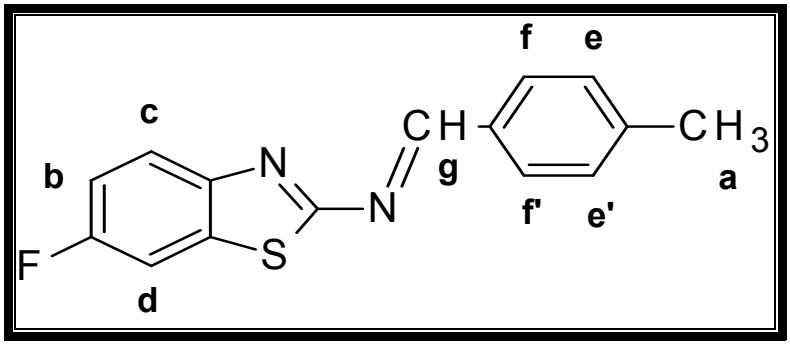


Table 2.4: ^{1}H NMR spectral data of 6-fluoro-N-[(Z)-(4-methylphenyl) methylidene]-1,3-benzothiazol-2-amine (BT-2).



Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	2.57	3H	Singlet	-C$\underline{H}_{3a}$	-
2	6.91-6.96	1H	Doublet	-C$\underline{H}_{b}$	-
3	7.28-7.31	1H	Singlet	-C$\underline{H}_{c}$	-
4	7.03	1H	Singlet	-C$\underline{H}_{d}$	-
5	7.51-7.55	2H	Doublet	Ar-$H_{ee'}$	8.96
6	7.96-7.99	2H	Doublet	Ar-$H_{ff'}$	7.84
7	8.52	1H	Singlet	Ar-H_{g}	-

Figure 2.3: Mass spectra of 6-fluoro-N-[(Z)-(4-methylphenyl)methylidene]-1,3-benzothiazol-2-amine (BT-2).

DEPARTMENT OF CHEMISTRY
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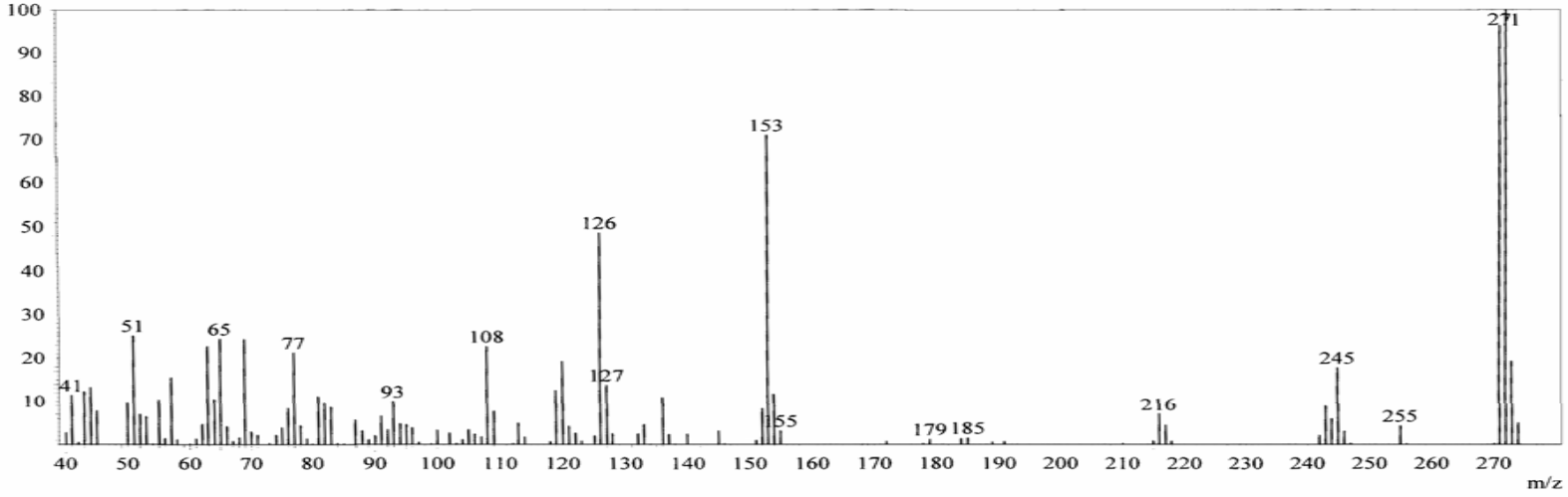
RAJKOT-360005

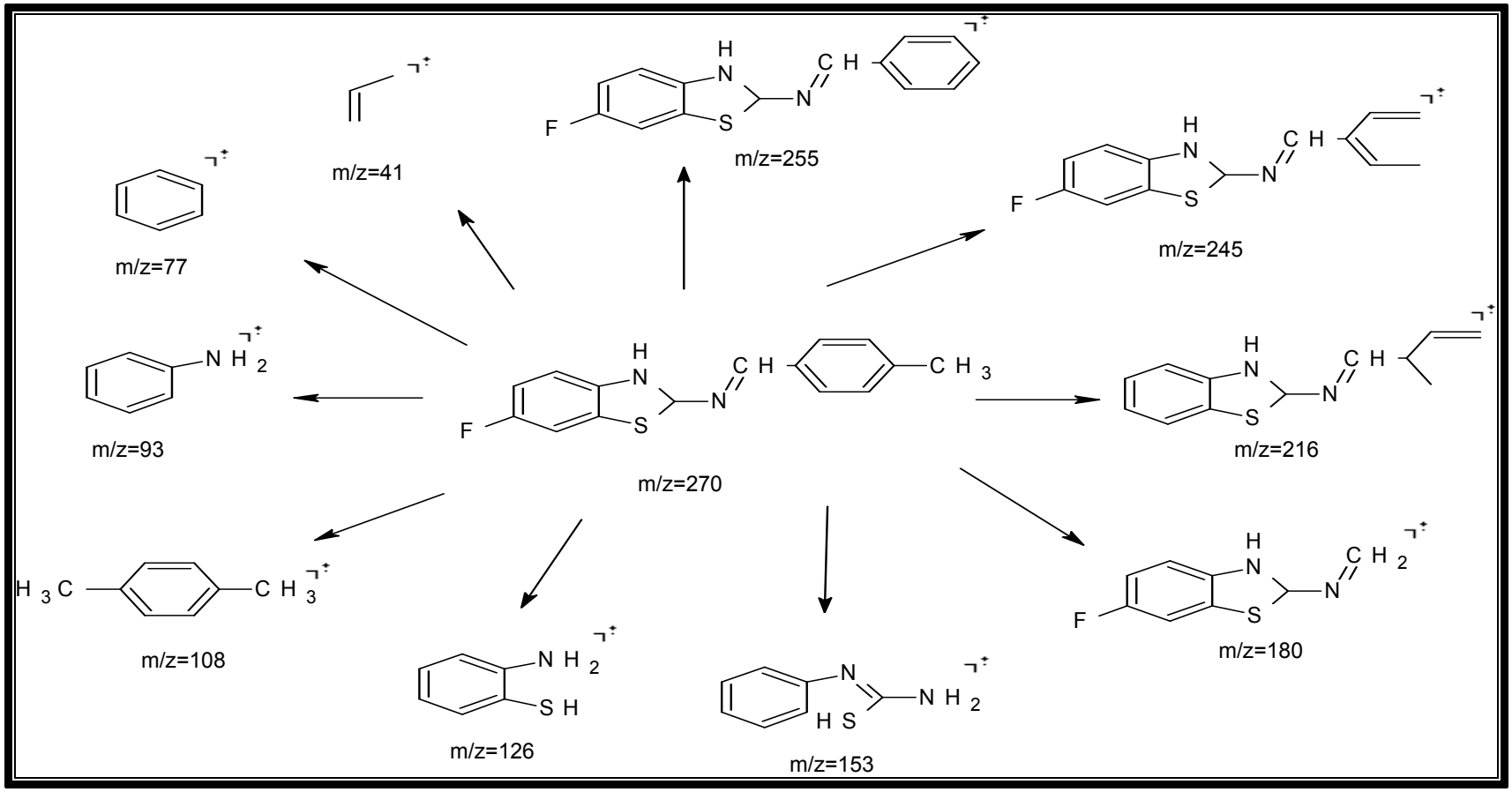
Sample Information

Analyzed by : VIJAY R. RAM
Analyzed : 5/9/2009 10:38:40 AM
Sample Name : BT-2
Sample ID : BT-2
Data File : C:\GCMSsolution\Data\Project1\BT-5.QGD
Method Name : C:\GCMSsolution\Data\Project1\DI.qgm

Line#:1 R.Time:7.1(Scan#:819)
MassPeaks:113 BasePeak:272(21949)
RawMode:Averaged 0.4-10.0(10-1167)
BG Mode:None



Scheme 2.1: Proposed mass fragmentation of 6-fluoro-N-[(Z)-(4-methylphenyl)methylidene]-1,3-benzothiazol-2-amine (BT-2).



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Chapter -3

Physico Chemical Properties

Section-I

Acoustical Properties

INTRODUCTION

Ultrasound waves are sound waves with a frequency greater than the upper limit of human hearing. Although this limit varies from person to person, it is approximately 20 kHz (20,000 hertz) and thus, 20 kHz serves as a useful lower limit in describing ultrasound. Some animals such as dogs, cats, dolphins, bats, and mice have an upper frequency limit that is greater than that of the human ear and thus can hear ultrasound.

Literature survey shows that these ultrasound waves have a number of applications in different fields[1-6] due to their non destructive nature. In medicine, it is used in non surgical removal of kidney stones[7], treatment of intracranial tumor[8], imaging fetal development during pregnancy[9]. In industry, these waves are used for large-scale cleaning[10], emulsification of cosmetics etc[11]. It is also used in food industry[12]. In engineering[13, 14], these waves are used for welding plastics[15], cutting alloys[16] etc.

The study of chemical effects of ultrasound is a rapidly growing research area[17-23]. Now a days, lots of interest has been generated on the use of ultrasound irradiation in synthetic organic chemistry, which cause decrease of reaction time, increase of yield, lower reaction temperature, avoidance of phase transfer catalysis etc[24, 25]. Various workers have reported some organic reactions through ultrasound irradiation. Srinivasan et al[26, 27] and Antunes et al[28] have reported some reactions using these waves.

This technique has also been used to study different materials[29], liquid crystals[30], cleavage[31] and structure of solids[32-35]. It is also useful to the synthesis of biodiesel[36]. Some of the most important aspects of sonochemistry have been its applications in the modification of both organic and inorganic materials[37, 38].

In physical chemistry, ultrasonic velocity measurements have been used to study the nature of molecular interactions in various binary[39-42], and ternary[43-47], and liquid mixtures[48-51]. However, little work has been done for solutions of solid organic compounds[52-58]. In recent years, various chemists synthesized different pyrimidine derivatives due to their biological importance but in our knowledge, no one has studied their acoustical properties.

Thus, with a view to understand the molecular interactions in solutions of dihydropyrimidinones, the present chapter deals with studies of various

acoustical and thermodynamic parameters of the solutions of dihydropyrimidinones in DMF and DMSO solutions at 298.15 K, over a wide range of concentration.

EXPERIMENTAL

The selected solvents DMF and DMSO for the present study are distilled by the reported procedure[59]. The synthesized compounds dihydropyrimidinones were recrystallized before use.

The densities and ultrasonic velocities of solvents and solutions of dihydropyrimidinones of different concentrations were measured at 298.15 K by using pyknometer and single frequency ultrasonic interferometer operating at 2 MHz, with the uncertainties of 0.0001 g/cm^3 and 0.01% respectively.

Density measurements:

The weight of distilled water, pure solvents and solutions of dihydropyrimidines were measured by using pyknometer. The densities (ρ) were evaluated by using following equation:

$$\rho\left(g/cm^3\right) = \frac{\left(\text{wt. of solvent or solution}\right)\left(\text{density of water}\right)}{\left(\text{wt. of water}\right)} \qquad \ldots (3.1.1)$$

Viscosity Measurements:

To determine the viscosity of solution, Ubbelohde viscometer[60] was used, which obeys Stoke's low[61]. The measured quantity of the distilled water / solvent / solution was placed in the viscometer, which was suspended in a thermostat at 298.15 K. The digital stopwatch, with an accuracy of $\pm$ 0.01 sec was used to determine flow time of solutions. Using the flow times (t) and known viscosity of standard water sample, the viscosity of solvent and solutions were determined according to equation:

$$\frac{\eta_1}{\eta_2} = \frac{t_1\rho_1}{t_2\rho_2} \qquad \ldots (3.1.2)$$

Sound velocity measurement:

Ultrasonic interferometer (Mittal Enterprise, New Delhi, Model No. F-81) working at frequency of 2 MHz was used to determine sound velocity.

The solvent / solution were filled in the measuring cell with quartz crystal and then micrometer was fixed. The circulation of water from the thermostat at 298.15 K was started and test solvent / solution in the cell is allowed to thermally equilibrate. The micrometer was rotated very slowly so as to obtain a maximum or minimum of anode current (n). A number of maximum reading of anode current were counted. The total distance (d) travel by the

micrometer for n=10, was read. The wave length (λ) was determined according to the equation (3.1.3).

$$\lambda = \frac{2d}{n} \qquad \ldots (3.1.3)$$

The sound velocity (U) of solvent and solutions were calculated from the wavelength and frequency (F) according to equation (3.1.4).

$$U = \lambda F \qquad \ldots (3.1.4)$$

where, F= 2×10^6 Hertz.

RESULTS AND DISCUSSION

Table 3.1.1 shows the experimental data of density (ρ), viscosity and sound velocity (U) of pure solvents and solutions of synthesized dihydropyrimidinones in DMF and DMSO at 298.15 K.

From these experimental data, various acoustical parameters like isentropic compressibility (κ_S), intermolecular free length (L_f), molar compressibility (W), Rao's molar sound function (R_m), Vander Waals constant (b), relaxation strength (r), apparent molar compressibility (ϕ_k) etc., were evaluated using the following equations:

1. Isentropic compressibility:

Isentropic compressibility (κ_s) was evaluated by Krishnamurty et al.[62]:

$$\kappa_s = \frac{1}{U^2 \rho} \qquad \ldots (3.1.5)$$

2. Intermolecular free path length:

The intermolecular free path length (L_f), was calculated by equation[63]:

$$L_f = K_j \kappa_s^{1/2} \qquad \ldots (3.1.6)$$

where K_J is Jacobson constant (=2.0965 X 10^{-6})

3. Molar compressibility:

Molar compressibility (W) can be calculated by the following equation[64]:

$$W = \left(\frac{M}{\rho} \right) \kappa_s^{-1/7} \qquad \ldots (3.1.7)$$

The apparent molecular weight (M) of the solution can be calculated as:

$$M = M_1 W_1 + M_2 W_2 \qquad \ldots (3.1.8)$$

where W_1 and W_2 are weight fractions of solvent and solute, respectively. M_1 and M_2 are the molecular weights of the solvent and compounds respectively.

Table 3.1.1: The density (*ρ*), ultrasonic velocity (*U*) and viscosity (*η*) of Dihydropyrimidinones in DMF and DMSO at 298.15 K

Conc. M	*Density ρ g.cm^{-3}*	*Velocity U. 10^{-5} cm.s^{-1}*	*Viscosity η.10^{3} poise*	*Density ρ g.cm^{-3}*	*Velocity U. 10^{-5} cm.s^{-1}*	*Viscosity η.10^{3} poise*
	DMF			***DMSO***		
	RVG-1			***RVG-1***		
0.00	0.9453	1.4516	8.4812	1.0959	1.4824	21.4335
0.01	0.9494	1.4552	9.2498	1.0971	1.4856	22.0260
0.02	0.9506	1.4580	9.3589	1.0982	1.4868	22.3210
0.04	0.9531	1.4604	9.7825	1.0989	1.4916	22.7872
0.06	0.9555	1.4656	10.0641	1.0998	1.4936	23.2742
0.08	0.9577	1.4676	10.2132	1.1004	1.4964	24.2054
0.10	0.9584	1.4688	10.3525	1.1012	1.4976	24.7118
	RVG-2			***RVG-2***		
0.01	0.9485	1.4640	8.9859	1.0971	1.4844	22.2629
0.02	0.9498	1.4648	9.0944	1.0987	1.4872	22.7605
0.04	0.9516	1.4660	9.3217	1.0992	1.4904	23.3450
0.06	0.9536	1.4668	9.5184	1.1005	1.4932	23.7469
0.08	0.9554	1.4676	9.7231	1.1017	1.4948	24.0041
0.10	0.9571	1.4680	9.9205	1.1023	1.4964	24.0916
	RVG-3			***RVG-3***		
0.01	0.9488	1.4548	9.0517	1.0965	1.4840	22.4517
0.02	0.949	1.4568	9.2779	1.0973	1.4852	22.7831
0.04	0.952	1.4584	9.5748	1.0994	1.4860	23.3055
0.06	0.9527	1.4604	9.7267	1.1009	1.4876	23.7051
0.08	0.9543	1.4612	9.9053	1.101	1.4904	24.0499
0.10	0.9565	1.4628	10.1104	1.1026	1.4924	24.5650
	RVG-4			***RVG-4***		
0.01	0.947	1.4536	9.5794	1.0974	1.4836	21.9817
0.02	0.9474	1.4556	9.7583	1.0982	1.4860	22.3051
0.04	0.9478	1.4572	9.8767	1.0992	1.4916	22.7033
0.06	0.9484	1.4588	10.0145	1.0996	1.4908	23.0670
0.08	0.9489	1.4604	10.1159	1.1010	1.4928	23.3952
0.10	0.9505	1.4624	10.3497	1.1027	1.4956	23.7239
	RVG-5			***RVG-5***		
0.01	0.9494	1.4536	9.0608	1.0969	1.4860	21.9783
0.02	0.9517	1.4548	9.2320	1.0985	1.4876	22.3748
0.04	0.953	1.4568	9.6159	1.0996	1.4888	22.8601
0.06	0.9555	1.4580	9.8382	1.1003	1.4904	23.1175
0.08	0.9577	1.4592	9.9568	1.1017	1.4920	23.3330
0.10	0.9597	1.4612	10.1686	1.1026	1.4964	23.5928

Conc. M	Density ρ $g.cm^{-3}$	Velocity U. 10^{-5} $cm.s^{-1}$	Viscosity η.10^{3} poise	Density ρ $g.cm^{-3}$	Velocity U. 10^{-5} $cm.s^{-1}$	Viscosity η.10^{3} poise
	DMF			DMSO		
	RVG-6			RVG-6		
0.00	0.9487	1.4572	9.1114	1.0959	1.4824	21.4335
0.01	0.9505	1.4608	9.3522	1.0972	1.4836	21.8904
0.02	0.9518	1.4636	9.4626	1.0982	1.4852	22.4203
0.04	0.9547	1.4656	9.6089	1.0995	1.4860	22.8885
0.06	0.9554	1.4672	9.7611	1.1007	1.4872	23.2733
0.08	0.9566	1.4684	10.2176	1.1011	1.4884	23.4584
0.10	0.9487	1.4572	9.1114	1.1028	1.4896	23.5611
	RVG-7			RVG-7		
0.01	0.9485	1.4536	9.0957	1.0978	1.4848	21.9738
0.02	0.95	1.4552	9.2487	1.0984	1.4864	22.1992
0.04	0.9515	1.4564	9.3988	1.0998	1.4888	22.6825
0.06	0.9528	1.4596	9.6162	1.1004	1.4900	22.8767
0.08	0.9535	1.4608	9.8153	1.1011	1.4916	23.3176
0.10	0.9546	1.4628	9.9936	1.1028	1.4936	23.6556
	RVG-8			RVG-8		
0.01	0.9505	1.4524	9.4348	1.0986	1.4860	22.2297
0.02	0.9523	1.4540	9.7076	1.0995	1.4880	22.5092
0.04	0.9558	1.4564	9.9335	1.1003	1.4896	22.8667
0.06	0.9581	1.4592	10.1655	1.1011	1.4908	23.3389
0.08	0.9587	1.4600	10.1857	1.103	1.4928	23.5840
0.10	0.9595	1.4616	10.6120	1.1044	1.4948	23.9550
	RVG-9			RVG-9		
0.01	0.9508	1.4540	9.2370	1.0982	1.4872	22.3634
0.02	0.9524	1.4548	9.4858	1.0986	1.4888	22.7426
0.04	0.9558	1.4564	9.5900	1.0998	1.4900	23.1083
0.06	0.9576	1.4572	9.8876	1.1006	1.4916	23.5672
0.08	0.9605	1.4592	10.0484	1.1013	1.4932	23.8665
0.10	0.9617	1.4608	10.1376	1.1021	1.4952	24.3731
	RVG-10			RVG-10		
0.01	0.9514	1.4548	8.9812	1.097	1.4836	21.8745
0.02	0.9536	1.4568	9.1308	1.0983	1.4848	22.1640
0.04	0.9558	1.4580	9.4032	1.0991	1.4856	22.3949
0.06	0.9578	1.4592	9.6990	1.0999	1.4880	22.7350
0.08	0.959	1.4616	9.8106	1.1007	1.4892	23.4778
0.10	0.9602	1.4628	10.0731	1.1013	1.4912	23.7483

4. Rao's molar sound function:

Rao's molar sound function (R_m) can be evaluated by an equation given by Bagchi et al.[65]:

$$R_m = \left(\frac{M}{\rho}\right) U^{1/3} \qquad \ldots (3.1.9)$$

5. Van der Waals Constant:

Van der Waals constant (b) can be calculated as follows[66]:

$$b = \frac{M}{\rho}\left\{1-\left(\frac{RT}{MU^2}\right)\left[\sqrt{1+\frac{MU^2}{3RT}}-1\right]\right\} \qquad \ldots(3.1.10)$$

where R is the gas constant (=8.3143 JK^{-1} mol^{-1}) and T is the absolute temperature.

6. Relaxation Strength:

The relaxation strength (r) can be calculated as follows[67]:

$$r = 1-\left[\frac{U}{U_\infty}\right]^2 \qquad \ldots (3.1.11)$$

where U_∞ = 1.6 x 10^5 cm/sec.

7. Solvation number:

The solvation number (S_n) can be calculated according to the equation[68]

$$S_n = \frac{M_2}{M_1}\left[\frac{1-\kappa_s}{\kappa_{s1}}\right]\left[\frac{100-X}{X}\right] \qquad \ldots(3.1.12)$$

where X is the number of grams of solute in 100 gm of the solution. M_1 and M_2 are the molecular weights and κ_{S1} and κ_S are isentropic compressibility of solvent and solute respectively.

8. Apparent Molar Compressibility (ϕ_k):

The apparent molar compressibility (ϕ_K) of the solutions was calculated by the following equation[69]:

$$\phi_K = \frac{\left(\rho_0\kappa_s - \rho\kappa_s^0\right)1000}{c\rho_0} + \frac{\kappa_s^0 M_2}{\rho_0} \quad \ldots (3.1.13)$$

where ρ_0 and κ_s^0 are density and isentropic compressibility of pure solvent respectively, c is the concentration of the solution and M_2 is the molecular weight of the compound.

Some of these calculated parameters are given in Table 3.1.2 for the studied compounds in DMF and DMSO respectively. Figure 3.1.1 show the variation of ultrasound velocity (U) with concentration in DMF and DMSO solutions. It is observed that overall ultrasonic velocity (U) increases with concentration for all the compounds in both the solvents. The velocity depends on intermolecular free length (L_f). The velocity increases with decrease in L_f or vice versa. It is evident from Table 3.1.2 that L_f decreases continuously, which suggests that there is strong interaction between solvent (both DMF and DMSO) and compound molecules.

This is further supported by isentropic compressibility (κ_s) and relaxation strength (r) values. The variation of isentropic compressibility (κ_s) with concentration of these compounds is also shown Figure 3.1.2 for all the solutions in both the solvents. The nature of curves is opposite to those of velocity (Fig. 3.1.1.). Both isentropic compressibility (κ_s) and relaxation strength (r) (Table 3.1.3) are observed to decrease with concentration for all the compounds. The decrease in isentropic compressibility is attributed to the fact that the dihydropyrimidinones (DHPMs) molecules in dilute solutions are considerably ionized and these ions are firmly bound to surrounding solvent molecules. The orientation of solvent molecules around the ions is attributed to the influence of the electrostatic field of the ions, which lowers the compressibility of the DHPMs solutions[70].

Figure 3.1.3 shows the linear variation of molar compressibility (W) with concentration whereas Table 3.1.3 show the variation of molar sound function (R_m) and Vander Waals constant (b) with concentration. All the three parameters varies linearly with concentration and the correlation coefficients are in the range of 0.9991- 0.9999. This linear change of these parameters suggests the absence of complex formation in these systems.

Table 3.1.3: Some acoustical parameters of Dihydropyrimidinones derivatives in DMF and DMSO at 298.15 K.

	DMF				DMSO			
Conc. M	L_f A^o	r	$R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$	b $cm^3.mol^{-1}$	L_f A^o	r	$R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$	b $cm^3.mol^{-1}$
	RVG-1				RVG-1			
0.00	0.1485	0.1769	4.0635	77.3176	0.1351	0.1416	4.5458	85.8912
0.01	0.1479	0.1728	4.1244	78.4103	0.1347	0.1379	4.5970	86.7962
0.02	0.1475	0.1696	4.1966	79.7326	0.1346	0.1365	4.6464	87.7052
0.04	0.1470	0.1669	4.3366	82.3471	0.1341	0.1309	4.7540	89.6395
0.06	0.1463	0.1609	4.4786	84.9431	0.1338	0.1286	4.8575	91.5510
0.08	0.1460	0.1587	4.6172	87.5326	0.1336	0.1253	4.9632	93.4838
0.10	0.1458	0.1573	4.7624	90.2604	0.1334	0.1239	5.0659	95.3932
	RVG-2				RVG-2			
0.01	0.1470	0.1628	4.1301	78.3607	0.1348	0.1393	4.5910	86.7053
0.02	0.1469	0.1619	4.1936	79.5521	0.1345	0.1360	4.6351	87.4831
0.04	0.1466	0.1605	4.3232	81.9877	0.1342	0.1323	4.7322	89.2517
0.06	0.1464	0.1596	4.4504	84.3850	0.1338	0.1290	4.8251	90.9469
0.08	0.1461	0.1587	4.5776	86.7819	0.1336	0.1272	4.9168	92.6429
0.10	0.1460	0.1582	4.7041	89.1708	0.1334	0.1253	5.0112	94.3876
	RVG-3				RVG-3			
0.01	0.1479	0.1733	4.1283	78.4930	0.1349	0.1397	4.5992	86.8676
0.02	0.1477	0.1710	4.2062	79.9362	0.1348	0.1384	4.6511	87.8255
0.04	0.1473	0.1692	4.3467	82.5768	0.1346	0.1374	4.7507	89.6901
0.06	0.1471	0.1669	4.4979	85.4093	0.1343	0.1356	4.8532	91.5929
0.08	0.1469	0.1660	4.6425	88.1393	0.1341	0.1323	4.9635	93.6143
0.10	0.1465	0.1641	4.7835	90.7845	0.1338	0.1300	5.0652	95.4911
	RVG-4				RVG-4			
0.01	0.1482	0.1746	4.1269	78.4869	0.1349	0.1402	4.5889	86.6813
0.02	0.1480	0.1724	4.1958	79.7602	0.1346	0.1374	4.6360	87.5238
0.04	0.1478	0.1705	4.3329	82.3373	0.1341	0.1309	4.7334	89.2517
0.06	0.1476	0.1687	4.4689	84.8904	0.1341	0.1318	4.8266	91.0258
0.08	0.1474	0.1669	4.6052	87.4473	0.1338	0.1295	4.9180	92.7064
0.10	0.1470	0.1646	4.7354	89.8795	0.1335	0.1262	5.0083	94.3501
	RVG-5				RVG-5			
0.01	0.1480	0.1746	4.1229	78.4103	0.1347	0.1374	4.5983	86.8122
0.02	0.1477	0.1733	4.1885	79.6371	0.1345	0.1356	4.6460	87.6807
0.04	0.1474	0.1710	4.3335	82.3564	0.1343	0.1342	4.7479	89.5799
0.06	0.1471	0.1696	4.4708	84.9431	0.1341	0.1323	4.8517	91.5067
0.08	0.1468	0.1683	4.6084	87.5326	0.1339	0.1304	4.9520	93.3641
0.10	0.1465	0.1660	4.7467	90.1192	0.1334	0.1253	5.0575	95.2595

	DMF				DMSO			
Conc. M	**L_f A^o**	**r**	**$R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$**	**b $cm^3.mol^{-1}$**	**L_f A^o**	**r**	**$R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$**	**b $cm^3.mol^{-1}$**
	RVG-6				**RVG-6**			
0.00	0.1477	0.1769	4.0635	77.3176	0.1351	0.1416	4.5458	85.8912
0.01	0.1472	0.1705	4.1311	78.5014	0.1349	0.1402	4.5958	86.8116
0.02	0.1468	0.1664	4.2031	79.8055	0.1347	0.1384	4.6472	87.7519
0.04	0.1464	0.1632	4.3528	82.5954	0.1345	0.1374	4.7503	89.6815
0.06	0.1462	0.1609	4.4928	85.2122	0.1344	0.1360	4.8538	91.6107
0.08	0.1460	0.1591	4.6428	88.0245	0.1342	0.1346	4.9608	93.6051
0.10	0.1477	0.1577	4.7891	90.7735	0.1340	0.1332	5.0610	95.4719
	RVG-7				**RVG-7**			
0.01	0.1481	0.1746	4.1219	78.3915	0.1348	1.0978	4.5896	86.6717
0.02	0.1478	0.1728	4.1867	79.5962	0.1346	1.0984	4.6379	87.5520
0.04	0.1476	0.1714	4.3206	82.1193	0.1343	1.0998	4.7325	89.2899
0.06	0.1471	0.1678	4.4568	84.6456	0.1341	1.1004	4.8291	91.0888
0.08	0.1470	0.1664	4.5936	87.2192	0.1339	1.1011	4.9256	92.8746
0.10	0.1467	0.1641	4.7286	89.7421	0.1337	1.1028	5.0173	94.5617
	RVG-8				**RVG-8**			
0.01	0.1481	0.1760	4.1341	78.6460	0.1346	0.1374	4.6037	86.9151
0.02	0.1478	0.1742	4.2194	80.2387	0.1344	0.1351	4.6673	88.0759
0.04	0.1472	0.1714	4.3878	83.3962	0.1342	0.1332	4.7960	90.4724
0.06	0.1468	0.1683	4.5607	86.6268	0.1340	0.1318	4.9240	92.8619
0.08	0.1467	0.1673	4.7397	90.0092	0.1337	0.1295	5.0470	95.1396
0.10	0.1464	0.1655	4.9179	93.3600	0.1335	0.1272	5.1719	97.4507
	RVG-9				**RVG-9**			
0.01	0.1479	0.1742	4.1343	78.6206	0.1345	0.1360	4.6067	86.9472
0.02	0.1477	0.1733	4.2197	80.2300	0.1344	0.1342	4.6721	88.1501
0.04	0.1472	0.1714	4.3878	83.3962	0.1342	0.1328	4.7987	90.5158
0.06	0.1470	0.1705	4.5613	86.6774	0.1340	0.1309	4.9273	92.9074
0.08	0.1466	0.1683	4.7286	89.8147	0.1338	0.1290	5.0561	95.3016
0.10	0.1463	0.1664	4.9037	93.1072	0.1336	0.1267	5.1846	97.6796
	RVG-10				**RVG-10**			
0.01	0.1477	0.1733	4.1247	78.4231	0.1349	0.1402	4.6024	86.9361
0.02	0.1474	0.1710	4.2007	79.8323	0.1347	0.1388	4.6578	87.9603
0.04	0.1471	0.1696	4.3588	82.8142	0.1346	0.1379	4.7746	90.1483
0.06	0.1468	0.1683	4.5165	85.7878	0.1343	0.1351	4.8927	92.3297
0.08	0.1465	0.1655	4.6788	88.8204	0.1342	0.1337	5.0093	94.5048
0.10	0.1463	0.1641	4.8390	91.8377	0.1340	0.1314	5.1276	96.6930

Figure 3.1.1: Variation of ultrasonic velocity (*U*) of Dihydropyrimidinones with concentration in [A] DMF and [B] DMSO at 298.15 K.

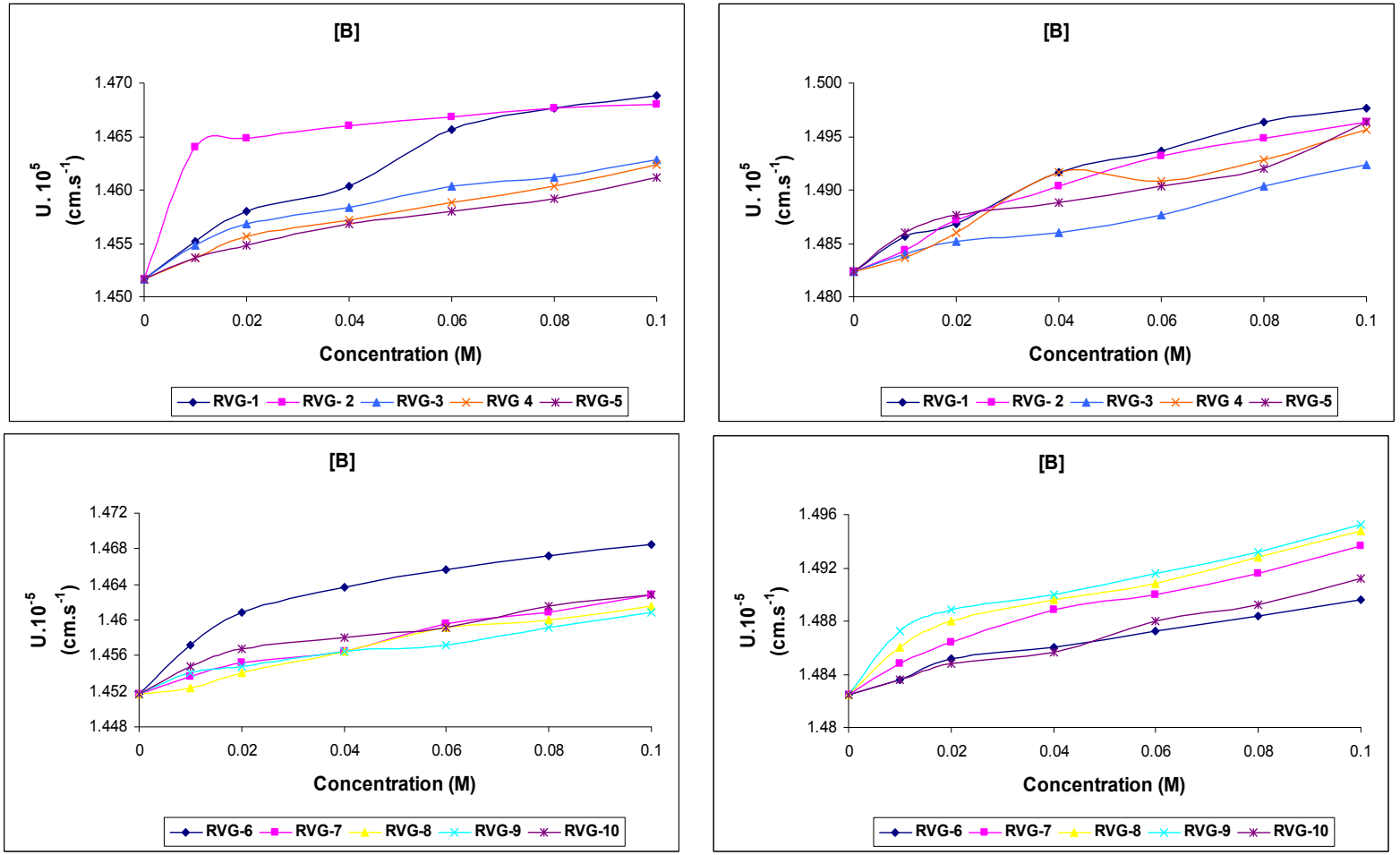


Figure 3.1.2: Variation of Isentropic compressibility (κ_s) of Dihydropyrimidinones with concentration in [A] DMF and [B] DMSO at 298.15 K.

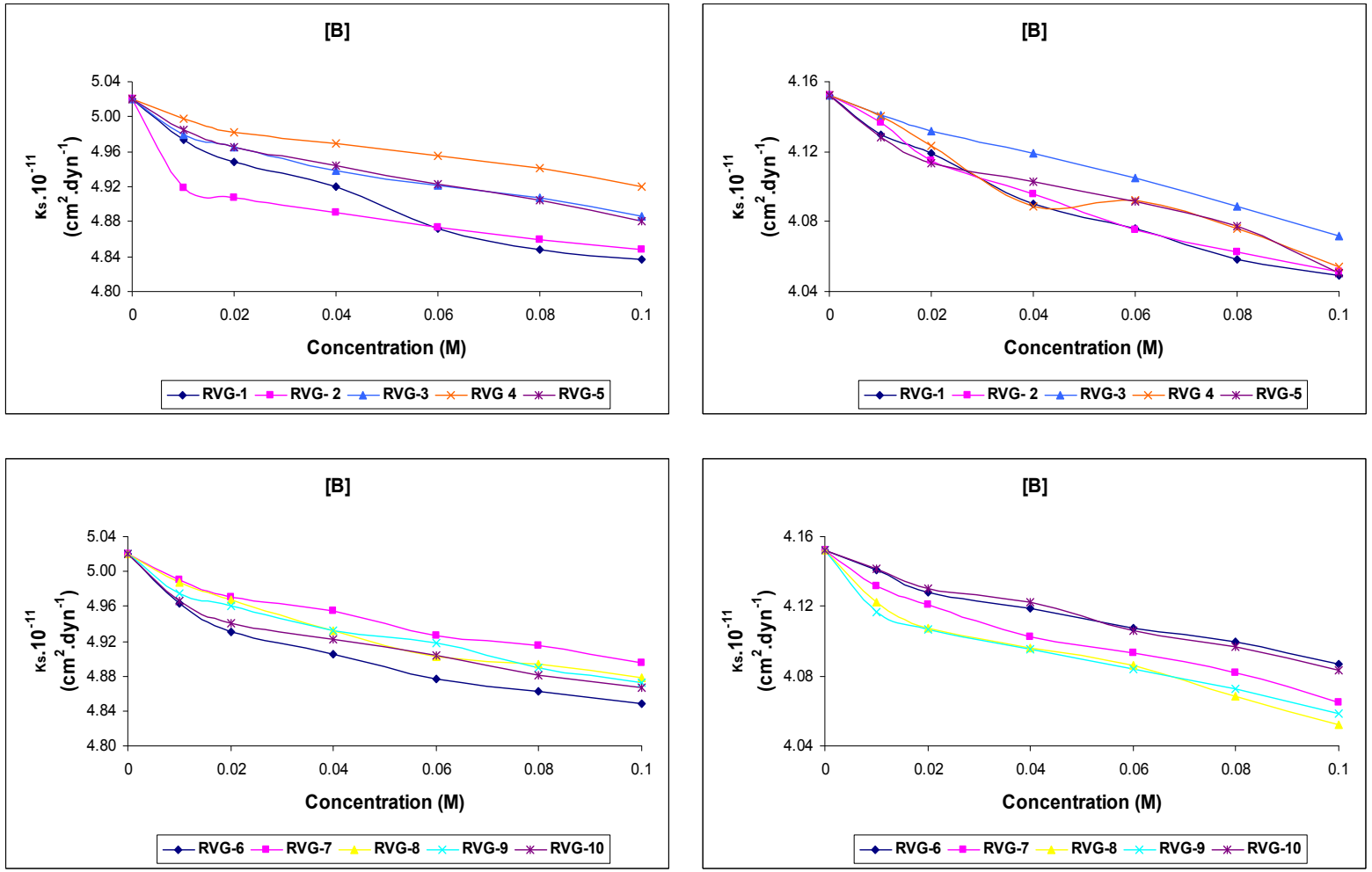
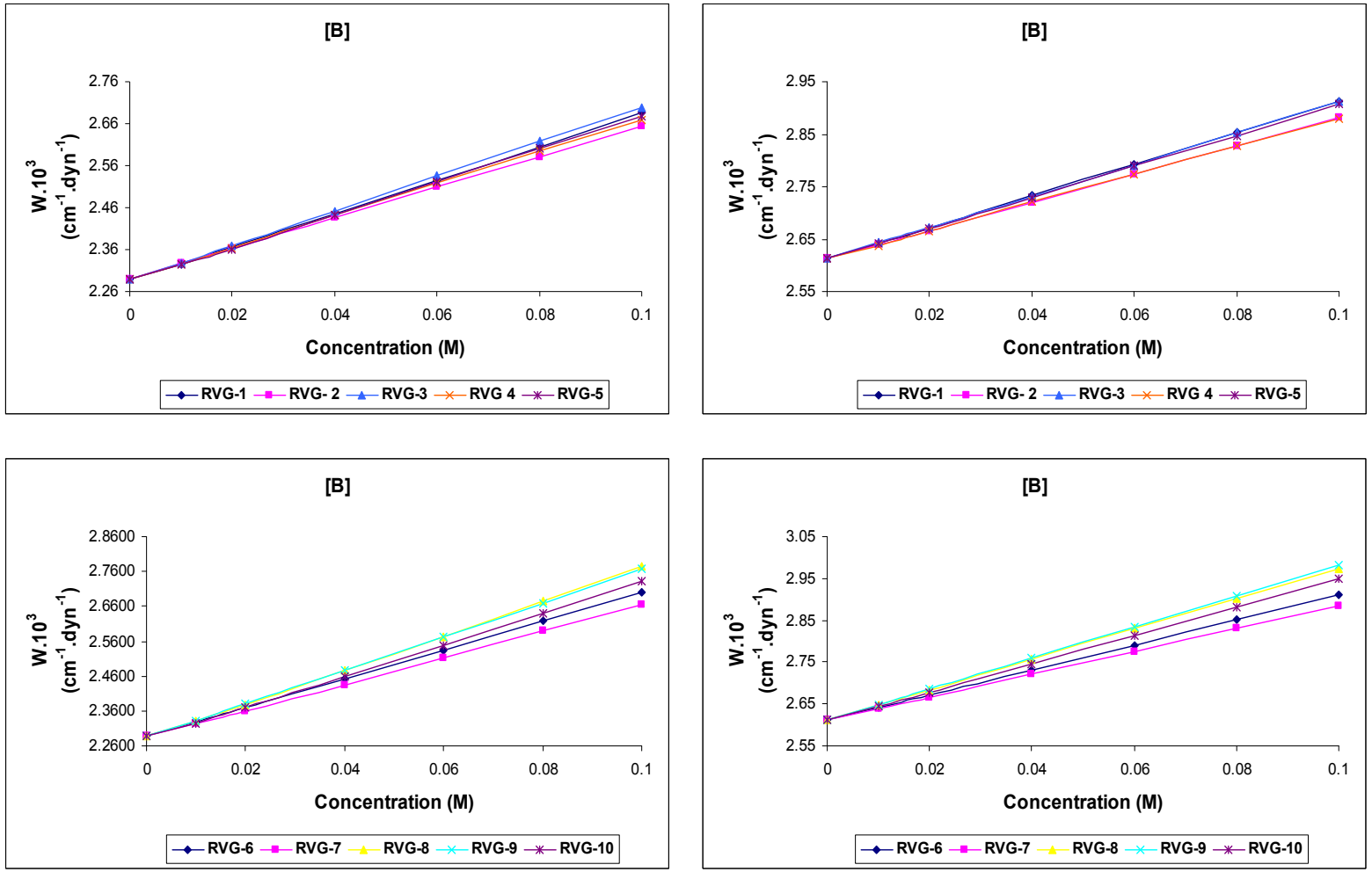


Figure 3.1.3: Variation of Molar compressibility (*W*) of Dihydropyrimidinones with concentration in [A] DMF and [B] DMSO at 298.15 K.



The interactions occurring in different solutions can also be confirmed by the solvation number, which is measure of structure forming or structure breaking tendency. Figure 3.1.4 show the variation of solvation number with concentration. For the studied compounds, S_n values are positive at low concentrations. The positive S_n is due to structure forming tendency whereas negative S_n suggests structure breaking tendency. In both the solvents, solvation number is found to increase with increasing concentration. However, in DMSO solutions, slight decrease in S_n is observed for RVG-2 and RVG-4 whereas for others there is increase at lower concentrations Thus, the overall finding suggests that the studied compounds exhibit solute-solvent interactions i.e. structure forming tendency of these compounds in both the solvents.

Figure 3.1.4: Variation of Solvation Number (S_n) of Dihydropyrimidinones with concentration in [A] DMF and [B] DMSO at 298.15 K.

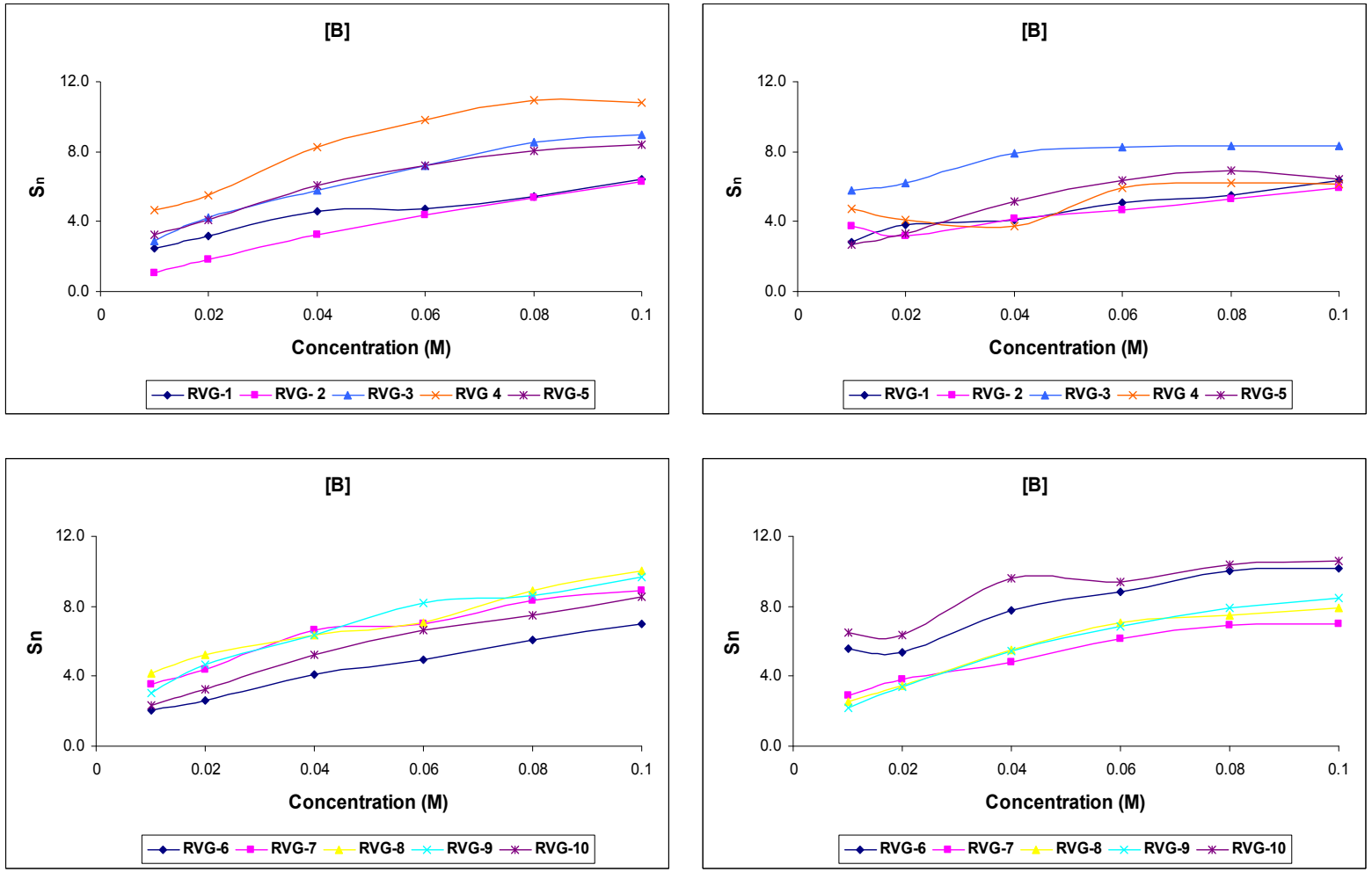


Table 3.1.4: Bachem's, Gucker's and Masson's constants of Dihydro pyrimidinones in DMF and DMSO at 298.15 K.

Compounds	A x 10^{11} dyn^{-1} cm^{-3} $.mol^{-1}$	B x 10^{11} dyn^{-1} $cm^{-1/2}$ $.mol^{-3/2}$	$\phi°_K$ x 10^8 $dyn^{-1}.mol^{-1}$	S_K x 10^8 dyn^{-1} $cm^{-3/2}$ $.mol^{-3/2}$	$\phi°_v$ $cm^3.mol^{-1}$	S_v $cm^3.mol^{-1}$
DMF						
RVG-1	-4.629	8.7972	-3.3025	8.8136	-252.31	1804.3
RVG-2	-4.8972	10.098	-39784	11.617	-113.15	817.66
RVG-3	-3.7944	8.242	-3.0021	10.745	-134	1205.1
RVG-4	-2.7633	6.2117	-2.0558	10.839	-6.4976	590.72
RVG-5	-3.6667	7.7383	-2.0841	6.5901	-155.94	988.95
RVG-6	-4.9163	10.2250	-4.1618	12.6530	-251.14	2563.6
RVG-7	-3.6717	8.3331	-1.7364	6.5383	-124.77	1227.8
RVG-8	-3.9725	8.3206	-3.8210	12.6430	-322.34	2859.3
RVG-9	-4.0006	8.4545	-2.0437	6.2675	-252.31	1804.3
RVG-10	-3.9775	7.874	-4.1675	13.1040	-268.76	2137.2
DMSO						
RVG-1	-2.742	5.6196	-1.3065	5.0384	-25.027	819.51
RVG-2	-1.8766	2.5988	-0.9653	3.5489	-0.5184	359.72
RVG-3	-1.3760	2.4847	-0.0474	1.8949	-7.6917	419.02
RVG-4	-1.3568	1.3155	-0.6134	2.9043	-57.559	1632.2
RVG-5	-2.8254	7.1072	-2.1338	9.1884	-10.126	450.73
RVG-6	-1.4248	2.7656	-0.0934	2.2183	-36.20	922.44
RVG-7	-2.2937	5.1411	-1.5367	6.7903	-50.07	1229.5
RVG-8	-2.1401	3.7012	-0.1466	1.4902	-29.19	514.72
RVG-9	-2.218	4.1876	-0.6994	3.7762	-6.98	492.23
RVG-10	-1.2705	1.9472	-0.1342	2.8083	-0.52	495.86

The isentropic compressibility of all the solutions was also fitted to the following Bachem's relation[71]:

$$\kappa_s = \kappa_{s1} + AC + BC^{3/2} \quad \ldots (3.1.14)$$

where *A* and *B* are constants, *C* is the molar concentration of DHPMs, and κ_S and κ_{S1} are the adiabatic compressibility of the solution and solvent respectively. The constants *A* and *B* have been determined from the intercept and slope of the plots of $(\kappa_S - \kappa_{S1})/C$ vs. $C^{1/2}$

Further, apparent molar compressibility and apparent molar volume of solutions are fitted to Gucker's[72] and Masson's[73] relations:

$$\phi_k = \phi_{\circ k} + S_k C^{1/2} \quad . \quad \ldots (3.1.15)$$

$$\phi_v = \phi^\circ_v + S_v C^{1/2} \quad \ldots (3.1.16)$$

where ϕ°_k and ϕ°_v are limiting apparent molar compressibility and limiting apparent molar volume, respectively. S_K and S_v are parameters for solute-solvent interactions. The values of ϕ°_k, ϕ°_v, and constants S_K and S_v, have been obtained from the intercept and slope of the plots of ϕ_k vs $C^{1/2}$ and ϕ_v vs $C^{1/2}$. All these constants are given in Table 3.1.4.

It is observed that for all the compounds in both the solvents, A values are negative whereas B values are positive. The negative A and positive B further confirms solute-solvent interactions in the studied system. This is further confirmed by negative ϕ°_k and ϕ°_v values.

The positive S_k and S_v confirms the existence of solute-solvent interactions in the studied systems.

Thus, it is concluded that DMF and DMSO solutions of dihydropyrimidinones exhibit solute-solvent interactions.

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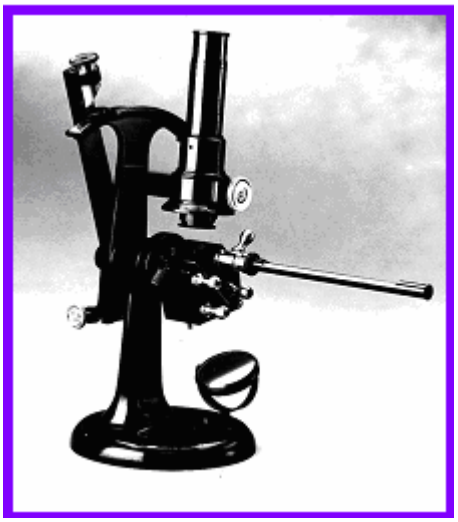


Section-II

Density and Refractive Index

INTRODUCTION

The refractive index of a substance is defined as the ratio of the velocity of light in vacuum to its velocity in the given medium. The refractive index of a material is the most important property of any optical system that uses refraction.

The refractive index plays a vital role in many branches of physics, biology and chemistry. Knowledge of the refractive index of aqueous solutions of salts and biological agents is of crucial importance in applications of evanescent wave techniques in biochemistry[1]. Chemical modifications may also be detected by measurements of refractive index[2]. Among the many possible applications is the control of adulteration of liquids[3].

It is used to calculate the focusing power of lenses, and the dispersive power of prisms. Since, refractive index is a fundamental physical property of a substance, it is often used to identify a particular substance, confirm its purity, or measure its concentration. For a solution of sugar, the refractive index can be used to determine the sugar content. A refractometer is the instrument used to measure refractive index.

Different methods have been developed to measure the refractive index of liquids. The most common type of refractometer measures the refractive index of the samples by detecting the critical angle of total reflection[4]. Many kinds of interferometric methods for determining the refractive index of materials have also been developed[5, 6].

Many workers have reported refractive index of oils[7, 8], amino acid[9], protein[10], sugar[11, 12], liquid crystals[13, 14], various gases [15], other materials[16, 17] etc. Further, much work has been done in liquid mixtures[18-30] but scanty work has been reported for the solutions of organic[31-33], inorganic[34-36] and polymeric materials[37-39].

Thus, in the present section, the refractive index of solutions of dihydropyrimidinones has been measured in dimethylformamide and dimethyl sulphoxide at 298.15 K. From the experimental data, the density and refractive index of the compounds have been evaluated.

EXPERIMENTAL

The solvents DMF and DMSO were purified by fractionally distillation by the reported method[39]. For each compound, a series of solutions of different concentrations were prepared in these solvents.

The density and refractive index of pure solvents and solutions were measured by using pycnometer and Abbe refrectometer respectively at 298.15 K. The temperature was maintained by circulating water through jacket around the prisms of refractometer from an electronically controlled thermostatic water bath (NOVA NV-8550 E). The uncertainty of temperature was ± 0.1 ^{o}C and that of density and refractive index was ± 0.0001 g/cm^{3} and 0.0005 respectively.

RESULTS AND DISCUSSION

The density of solution (ρ_{12}) is related to densities of the solvent, solute and their weight fractions g_1 and g_2 according to the equation:

$$\frac{1}{\rho_{12}} = \frac{g_1}{\rho_1} + \frac{g_2}{\rho_2} \qquad \ldots (3.2.1)$$

where ρ_{12} is the density of solution and ρ_1 and ρ_2 are the densities of solvent and solute respectively. Tables 3.2.1 and 3.2.2 show the experimental values of densities and refractive index for all the studied solutions.

The density of these compounds was determined from the slope of the plot of $1/g_1\rho_{12}$ verses g_2/g_1. Figure 3.2.1 shows the plot of $1/g_1\rho_{12}$ verses g_2/g_1 for RVG-1 in DMF and DMSO respectively. The inverse of slope gives the value of ρ_2. The densities of all the compounds (ρ_2) evaluated from such plots are given in Table 3.2.3 in DMF and DMSO solutions. Further, the density of compounds were evaluated by using the following equation (3.2.2),

$$\rho = KM/N_A \sum \Delta V_i \qquad \ldots (3.2.2)$$

where ρ is the density of the compound, *K* is packing fraction (0.599), M is the molecular weight of the compound, N_A is the Avogadro's number and ΔV_i is the volume increment of the atoms and atomic groups present in the compound. The densities of all the studied compounds have been evaluated and are reported in Table 3.2.3. The calculated volume increment ΔV_i for different atomic groups are given in Table 3.2.4.

Comparison of densities evaluated from graphs and those calculated from eq. (3.2.2) showed that calculated values are different from those evaluated graphically. Further, for the same compound, density in the two solvents is different. This suggests that solvent plays an important role. In solutions, molecular interactions exist which differ in different solvents. These interactions differ due to different substitutions in compounds. The presence of these interactions has also observed in ultrasonic studies which are discussed in section I of chapter 2. Due to these interactions, there may be some changes in volume which affects density.

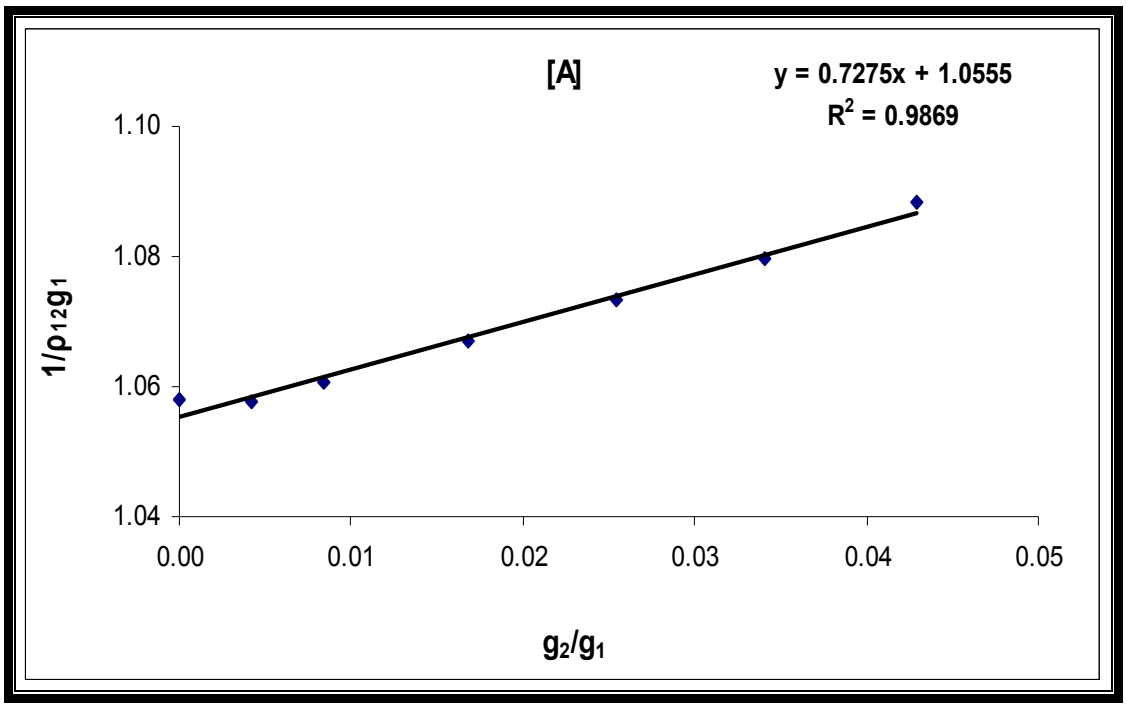
Table 3.2.1: The density (ρ_{12}) and refractive index (n) of Dihydro pyrimidinones in DMF at 298.15K.

Conc. M	ρ_{12} g.cm^{-3}	n	ρ_{12} g.cm^{-3}	n
	RVG-1		RVG-6	
0.00	0.9453	1.4218	0.9453	1.4218
0.01	0.9494	1.4261	0.9487	1.4219
0.02	0.9506	1.4274	0.9505	1.4227
0.04	0.9531	1.4291	0.9518	1.4233
0.06	0.9555	1.4308	0.9547	1.4249
0.08	0.9577	1.4321	0.9554	1.4259
0.10	0.9584	1.4336	0.9566	1.4273
	RVG-2		RVG-7	
0.01	0.9485	1.4237	0.9485	1.4222
0.02	0.9498	1.4248	0.9500	1.4229
0.04	0.9516	1.4257	0.9515	1.4236
0.06	0.9536	1.4275	0.9528	1.4241
0.08	0.9554	1.4283	0.9535	1.4256
0.10	0.9571	1.4308	0.9546	1.4269
	RVG-3		RVG-8	
0.01	0.9488	1.4223	0.9505	1.4219
0.02	0.9490	1.4231	0.9523	1.4224
0.04	0.9520	1.4235	0.9558	1.4230
0.06	0.9527	1.4241	0.9581	1.4236
0.08	0.9543	1.4249	0.9587	1.4241
0.10	0.9565	1.4265	0.9595	1.4249
	RVG -4		RVG-9	
0.01	0.9470	1.4219	0.9508	1.4224
0.02	0.9474	1.4226	0.9524	1.4232
0.04	0.9478	1.4231	0.9558	1.4239
0.06	0.9484	1.4238	0.9576	1.4252
0.08	0.9489	1.4249	0.9605	1.4268
0.10	0.9505	1.4255	0.9617	1.4281
	RVG -5		RVG-10	
0.01	0.9223	1.4225	0.9514	1.4221
0.02	0.9238	1.4234	0.9536	1.4227
0.04	0.9248	1.4243	0.9558	1.4234
0.06	0.9268	1.4253	0.9578	1.4241
0.08	0.9285	1.4258	0.9590	1.4248
0.10	0.9305	1.4283	0.9602	1.4256

Table 3.2.2: The density (ρ_{12}) and refractive index (n) of Dihydropyrimidinones in DMSO at 298.15K.

Conc. M	ρ_{12} g.cm^{-3}	n	ρ_{12} g.cm^{-3}	n
	RVG-1		RVG-6	
0.00	1.0959	1.4716	1.0959	1.4716
0.01	1.0971	1.4719	1.0972	1.4732
0.02	1.0982	1.4729	1.0982	1.4741
0.04	1.0989	1.4733	1.0995	1.4747
0.06	1.0998	1.4739	1.1007	1.4753
0.08	1.1004	1.4745	1.1011	1.4764
0.10	1.1012	1.4779	1.1028	1.4781
	RVG-2		RVG-7	
0.01	1.0971	1.4722	1.0978	1.4726
0.02	1.0987	1.4729	1.0984	1.4734
0.04	1.0992	1.4732	1.0998	1.4743
0.06	1.1005	1.4739	1.1004	1.4751
0.08	1.1017	1.4746	1.1011	1.4764
0.10	1.1023	1.4759	1.1028	1.4779
	RVG-3		RVG-8	
0.01	1.0965	1.4728	1.0986	1.4726
0.02	1.0973	1.4733	1.0995	1.4735
0.04	1.1002	1.4741	1.1003	1.4743
0.06	1.1009	1.4749	1.1011	1.4758
0.08	1.1010	1.4762	1.1030	1.4771
0.10	1.1026	1.4779	1.1044	1.4784
	RVG -4		RVG-9	
0.01	1.0974	1.4728	1.0982	1.4719
0.02	1.0982	1.4735	1.0986	1.4725
0.04	1.0992	1.4748	1.0998	1.4731
0.06	1.0996	1.4762	1.1006	1.4739
0.08	1.1010	1.4778	1.1013	1.4746
0.10	1.1027	1.4783	1.1021	1.4756
	RVG -5		RVG-10	
0.01	1.0969	1.4719	1.0970	1.4719
0.02	1.0985	1.4723	1.0983	1.4725
0.04	1.0996	1.4729	1.0991	1.4731
0.06	1.1003	1.4741	1.0999	1.4739
0.08	1.1017	1.4749	1.1007	1.4746
0.10	1.1036	1.4756	1.1013	1.4756

Figure 3.2.1: The variation of $1/g_1\rho_{12}$ with g_2/g_1 for RVG-1 in [A] DMF and [B] DMSO at 298.15 K.



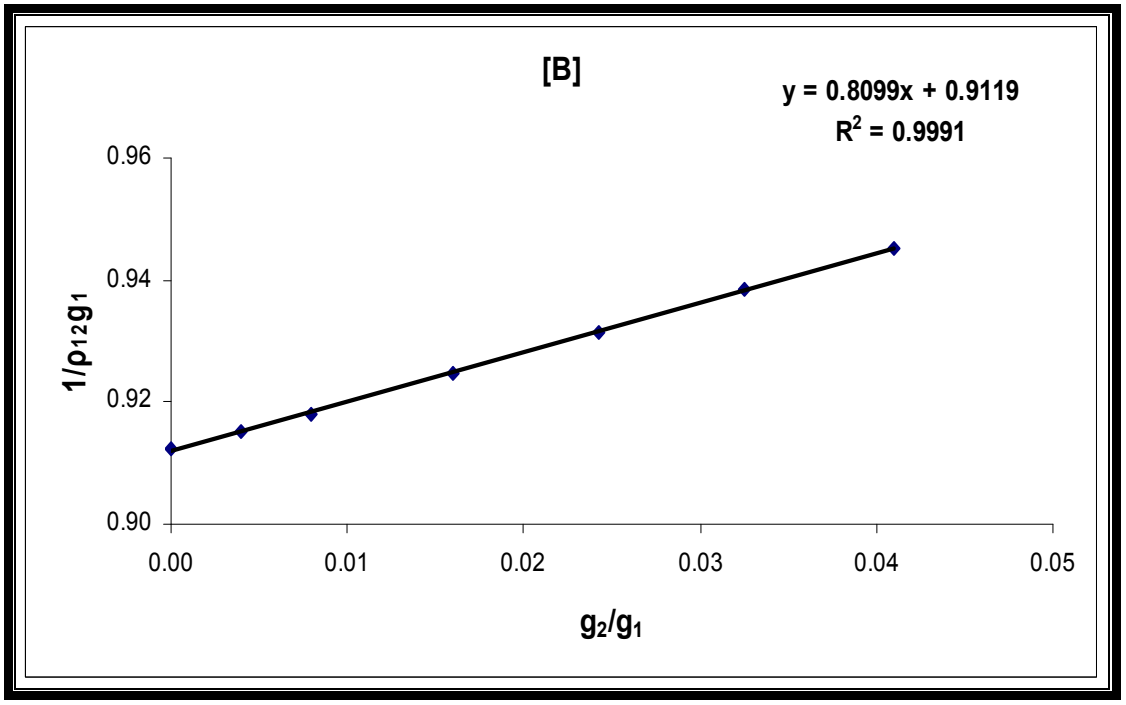
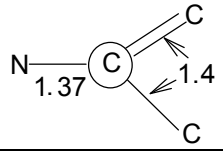
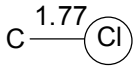
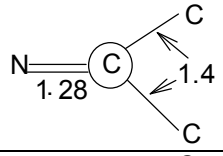
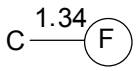
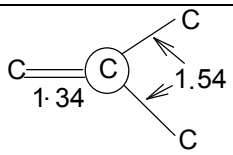
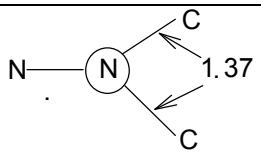
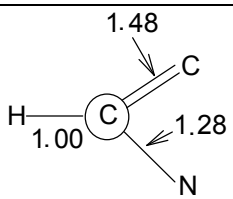
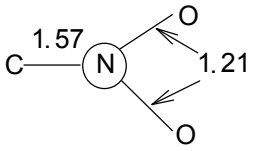
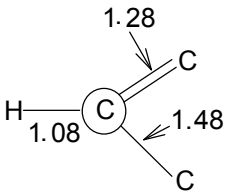
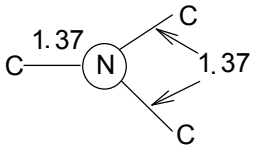
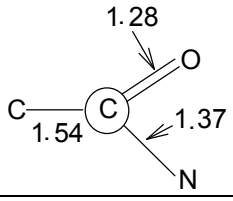
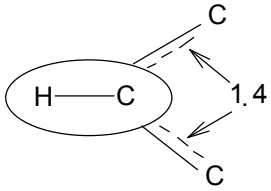
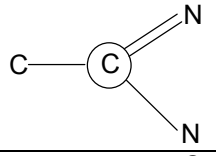
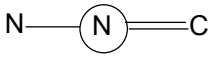
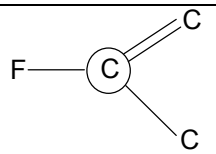
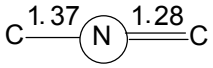
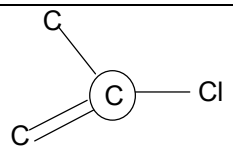
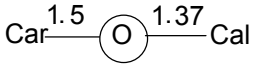


Table 3.2.3: Experimental and calculated densities of Dihydropyrimidinones in DMF and DMSO Solutions at 298.15 K.

Compounds	Density ($g.cm^{-3}$) calculated from Figure 3.2.1		Density ($g.cm^{-3}$) Calculated from Eq^{n}. 3.2.2
	DMF	***DMSO***	
RVG-1	1.3746	1.2347	1.0526
RVG-2	1.3226	1.3201	1.0749
RVG-3	1.2560	1.3168	1.1127
RVG-4	1.0622	1.3006	1.0749
RVG-5	1.1847	1.3355	1.0526
RVG-6	1.2962	1.3029	1.1319
RVG-7	1.2596	1.2999	1.1127
RVG-8	1.3454	1.3186	1.1588
RVG-9	1.3263	1.2204	1.1588
RVG-10	1.3939	1.1790	1.1695

Table 3.2.4: Volume increments of some atoms and groups of atoms.

Atoms or Atomic group	Volume Increments $(A^o)^3$	Atoms or Atomic group	Volume Increments $(A^o)^3$
	10.2		19.35
	7.84		9.2
	9.0		2.89
	3.61		7.46
	11.36		0.9
	14.10		14.7
	10.47		5.093
	11.40		5.62
	10.39		2.67

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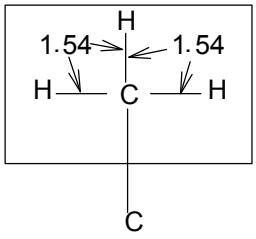
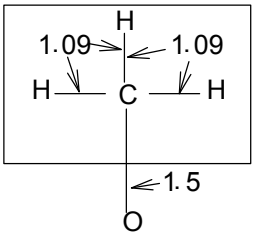
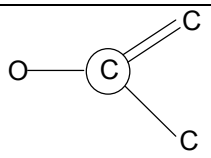
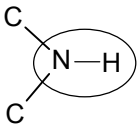
	23.5		26.3
	11.65		8.3

Further, the molar refraction of a pure liquid $(MRD)_1$ were calculated by the following equation:

$$\left(MRD\right)_1 = \left[\frac{n^2 - 1}{n^2 + 1}\right]\frac{M}{\rho} \qquad \ldots (3.2.3)$$

where n, M and ρ are refractive index, molecular weight and density of pure liquid respectively.

For solutions, following equation was used to determine molar refraction.

$$\left(MRD\right)_{12} = \left[\frac{n_{12}^2 - 1}{n_{12}^2 + 1}\right]\left[\frac{X_1 M_1 + X_2 M_2}{\rho_{12}}\right] \qquad \ldots (3.2.4)$$

where n_{12} and ρ_{12} are refractive index and density of solution respectively. X_1 and X_2 are the mole fractions and M_1 and M_2 are the molecular weight of the solvent and solute respectively.

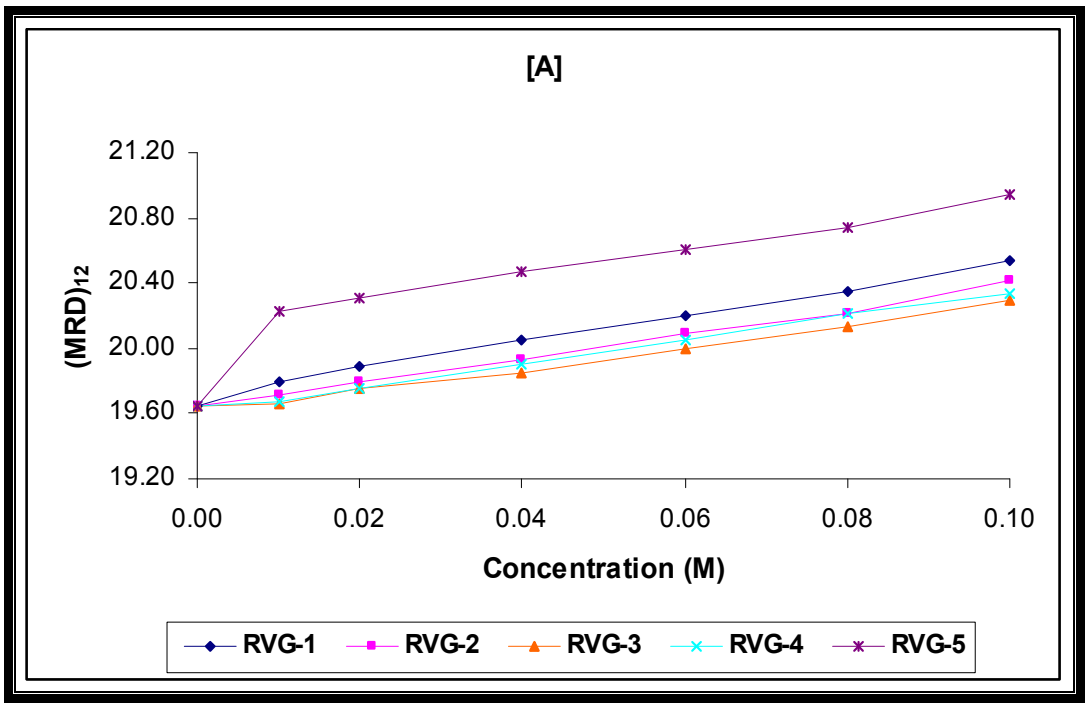
The plots of $(MRD)_{12}$ verses concentration for dihydropyrimidines series in DMF and DMSO are given in Figures 3.2.2 and 3.2.3 respectively. It is evident from these figures that $(MRD)_{12}$ increase with the increase in concentration. From the values of the molar refraction of solution and pure solvent, molar refraction of solid compounds were determined by following equation:

$$\left(MRD\right)_{12} = X_1\left(MRD\right)_1 + X_2\left(MRD\right)_2 \qquad \ldots (3.2.5)$$

From the density and molar refraction data, the refractive indexes of all the compounds were calculated from eq. (3.2.3). The molar refraction $(MRD)_2$ and refractive index of all the compounds are reported in Table 3.2.5 for 0.1 M solution.

It is evident from Table 3.2.5 that both $(MRD)_2$ and refractive index of compounds are different in each solvent. This again confirms different inter molecular interactions in different solvents. In some solvents, aggregation or hydrogen bonding takes place whereas in others, breakage of bonds takes place.

Figure 3.2.2: The plots of molar refraction *(MRD)*$_{12}$ against concentration of Dihydropyrimidinones in DMF solutions at 298.15 K.



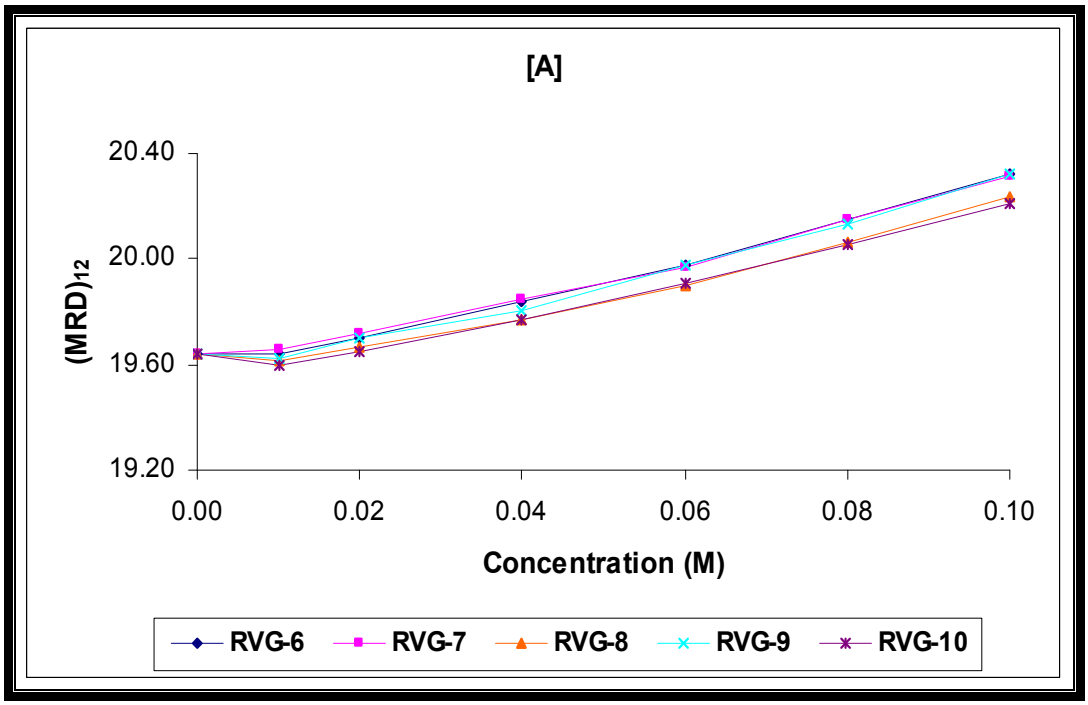
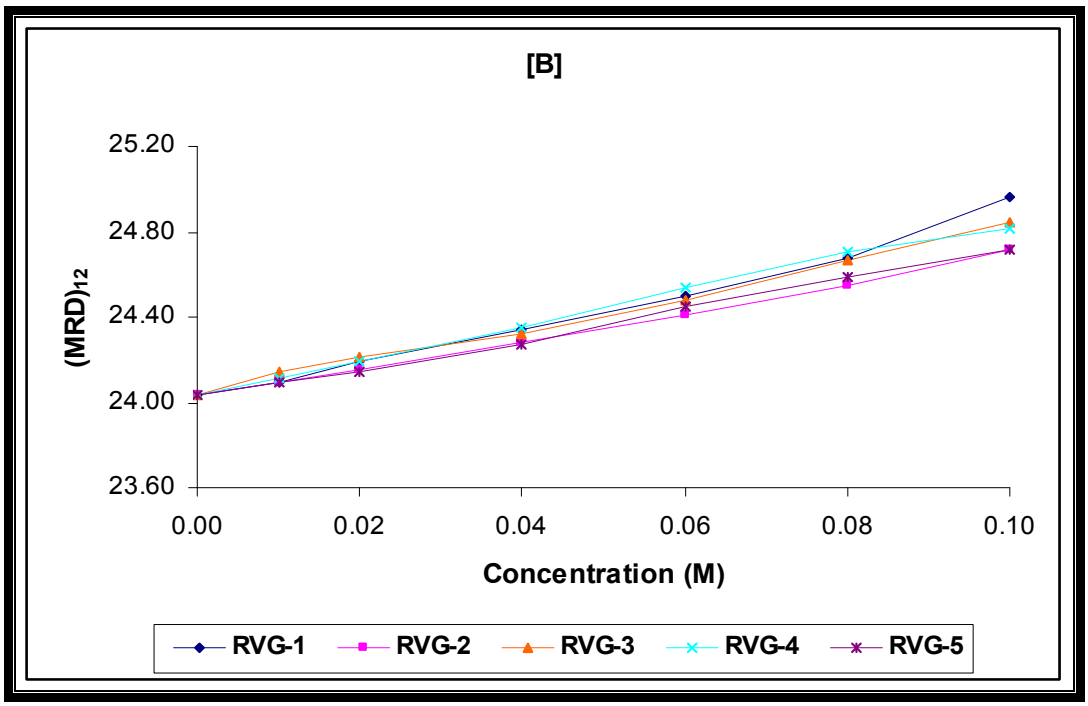


Figure 3.2.3: The plots of molar refraction $(MRD)_{12}$ against concentration of Dihydropyrimidinones in DMSO solutions at 298.15 K.



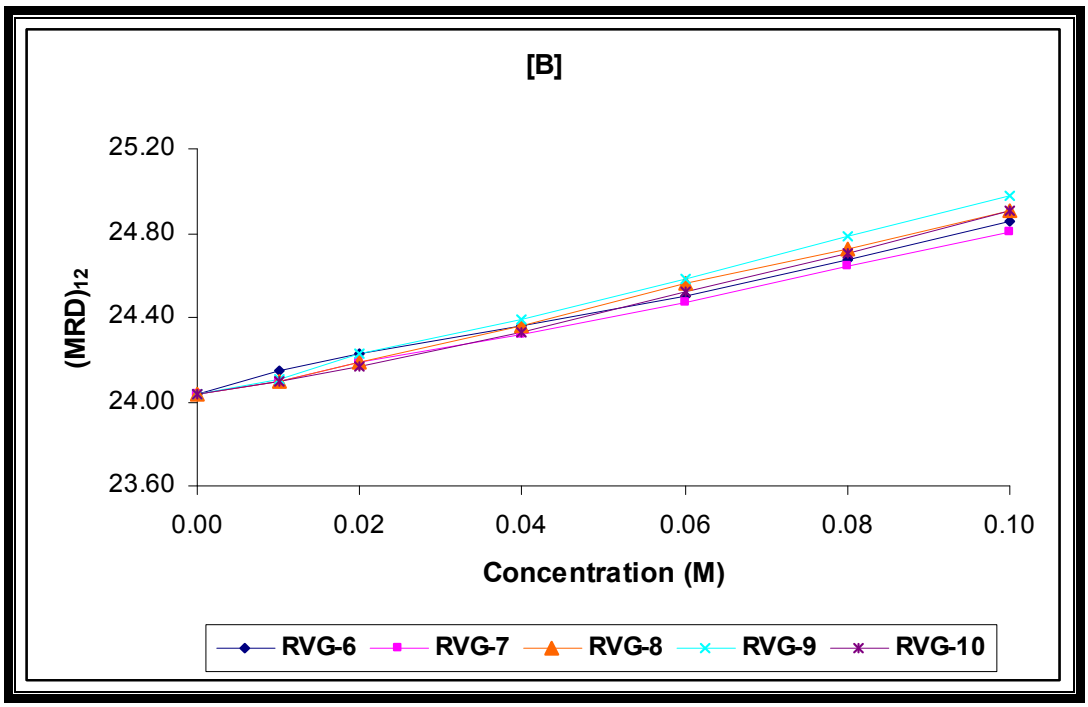


Table 3.2.5: Molar refraction *(MRD)$_2$* and refractive index *(n)* of 0.1M solution of Dihydropyrimidinones in DMF and DMSO at 298.15 K.

Compounds	*Solvents*			
	DMF		*DMSO*	
	(MRD$_2$)	*n*	*(MRD$_2$)*	*n*
RVG-1	133.61	1.4336	129.88	1.4779
RVG-2	118.08	1.4308	102.81	1.4759
RVG-3	102.37	1.4265	117.35	1.4779
RVG-4	107.93	1.4255	114.02	1.4783
RVG-5	181.09	1.4283	102.03	1.4756
RVG-6	106.33	1.4273	117.85	1.4781
RVG-7	105.32	1.4269	112.75	1.4779
RVG-8	95.20	1.4249	124.21	1.4784
RVG-9	106.18	1.4281	131.64	1.4787
RVG-10	92.44	1.4256	113.55	1.4756

Further, different compounds have different substitutions with the same central moiety. So, $(MRD)_2$ and refractive index values in Table 3.2.5 suggest that substitutions affect molar refractions to a larger extent than the refractive index, which changes only slightly.

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Section-III

Conductance

INTRODUCTION

Conductance is the ease with which current flows through a conductor. In solutions, ions conduct electricity so the conductance of such electrolytic solutions depends on the concentration of the ions and also on the nature of the ions present (through their charges and mobilities). The conductance behavior as a function of concentration is different for strong and weak electrolytes. Both strong and weak electrolytes will be studied at a number of dilute concentrations[1-5], and the ionization constant for a weak electrolyte can be calculated from the data obtained[6-8].

Conductivity measurement has widespread use in industrial applications that involve the detection of contaminants in water and concentration measurements[9]. Conductance measurements have been used for the determination of the equilibrium constants, degree of hydrolysis, dissociation constants and other properties of electrolyte solutions. Since all ions present in the solution contribute to the conductance process, conductance is an additive property of a solution depending on all the ions present. In acid-base titrations, this technique is also useful to determine relative strength of the two weak acids or bases, degree of hydrolysis, basicity of organic acid etc.

Literature survey shows that conductance of many organic, inorganic, polymers, rare earth, amino acid, vitamin etc. have been measured[10-22]. Further, the conductivity measurements have been used in liquid mixtures such as binary and ternary[23-28] Many workers have been reported the conductance of organic synthetic compounds[29-35] However, the conductivity data was not available for 1, 4 dihydropyrimidines.

Thus, in the present section conductance of all the synthesized 1, 4 dihydropyrimidines was measured in DMF and DMSO solutions at 298.15 K, over a wide range of concentration.

EXPERIMENTAL

The solvents DMF and DMSO were purified by fractionally distillation by the method reported in the literature[36].

The solutions of different concentrations were prepared for each compound in DMF and DMSO and the conductance of each solution was measured by using Equip-tronics Conductivity Meter (Model No. 664) having cell constant 0.96 cm^{-1} at 298.15 K. The measured conductance was corrected by subtracting the conductance of pure solvent.

RESULTS AND DISCUSSION

The measured conductance (k) of each solution after correction was used to determine the specific conductance (κ), which is then used for the calculation of equivalent conductance (λ_c).

The equations used for calculating specific conductance (κ) and equivalent conductance (λ_c) are:

$$\kappa = k\theta \qquad \ldots (3.3.1)$$

$$\lambda_c = 1000\frac{\kappa}{C} \qquad \ldots (3.3.2)$$

where θ is the cell constant (= 0.96 cm^{-1}) and c is the concentration (g.equi./lit.) of solution.

Tables 3.3.1 and 3.3.2 show the equivalent conductance of all the studied compounds in DMF and DMSO solutions at 298.15 K along with measured conductance (k). The variation of conductance with concentration for these compounds in both the solvents is given in Figures 3.3.1 and 3.3.2. For studied compounds, conductivities are observed to be less in DMSO than those in DMF. Further, for all the studied systems, conductance increases with concentration.

The equivalent conductance (λ_c) is plotted against $\sqrt{C}$ for all studied compounds and is shown in Figures 3.3.3 and 3.3.4. In both DMF and DMSO solutions, usually λ_c increases with dilution. But for certain compounds in DMSO solutions, λ_c do not increase continuously but bend downward at low concentrations giving rise to maximum. This typical behavior may be due to interactions within the molecule thereby causing constriction within the molecule or due to association between solute with solvent molecules. Similar behavior was observed by Prasad et al[37] while studying conductance of polyions in DMSO solutions. Further, it is evident from these figures that some compounds behave as strong electrolytes whereas most of them exhibited weak electrolytic behavior. The behavior is different in both the solvents.

For the systems where λ_c values increase with dilution, λ_0 values were evaluated by extrapolation. These values are compared with those determined by an alternate procedure using the following equation:

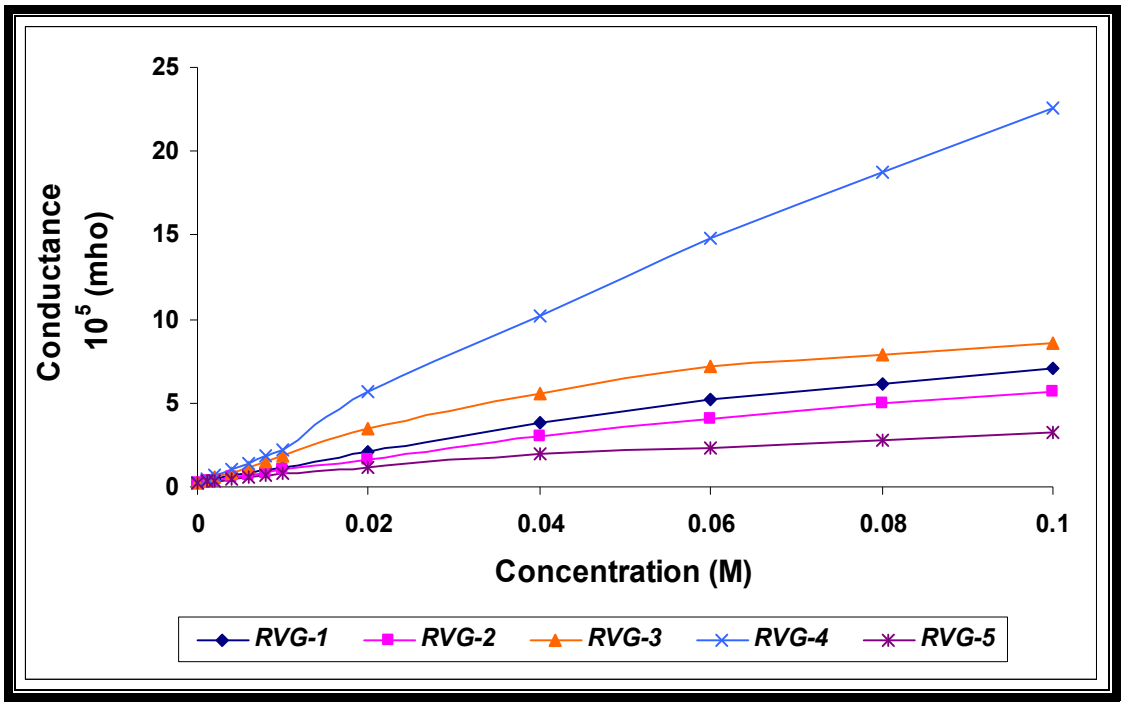
Table 3.3.1: The Conductance (*k*) and equivalent conductance (λ_C) of Dihydropyrimidines in DMF at 298.15 K.

Conc. M	***k.10^5 mho***	***λ_C mho.cm^2.equi.$^{-1}$***	***k.10^5 mho***	***λ_C mho.cm^2.equi.$^{-1}$***	***k.10^5 mho***	***λ_C mho.cm^2.equi.$^{-1}$***	***k.10^5 mho***	***λ_C mho.cm^2.equi.$^{-1}$***	***k.10^5 mho***	***λ_C mho.cm^2.equi.$^{-1}$***
	RVG-1		***RVG-2***		***RVG-3***		***RVG-4***		***RVG-5***	
0.000	0.20	-	0.20	-	0.20	-	0.20	-	0.20	-#DIV/0!
0.001	0.39	1.7376	0.32	1.0656	0.40	1.8912	0.42	2.0448	0.30	0.9312
0.002	0.46	1.2336	0.39	0.8976	0.53	1.5844	0.64	2.1024	0.35	0.7200
0.004	0.67	1.1280	0.53	0.7824	0.84	1.5192	0.99	1.8912	0.49	0.6744
0.006	0.86	1.0432	0.68	0.7632	1.20	1.5952	1.41	1.9296	0.59	0.6224
0.008	0.99	0.9456	0.86	0.7896	1.49	1.5432	1.82	1.9392	0.69	0.5844
0.010	1.18	0.9370	1.07	0.8314	1.84	1.5706	2.19	1.9066	0.81	0.5856
0.020	2.14	0.9293	1.67	0.7037	3.42	1.5437	5.70	2.6381	1.15	0.4541
0.040	3.83	0.8702	3.06	0.6854	5.56	1.2854	10.20	2.3990	1.92	0.4118
0.060	5.19	0.7978	4.10	0.6234	7.23	1.1242	14.80	2.3354	2.36	0.3450
0.080	6.18	0.7171	4.95	0.5695	7.82	0.9139	18.80	2.2315	2.75	0.3055
0.100	7.03	0.6553	5.70	0.5276	8.52	0.7983	22.60	2.1500	3.20	0.2876
	RVG-6		***RVG-7***		***RVG-8***		***RVG-9***		***RVG-10***	
0.001	0.31	1.0176	0.42	2.0736	0.32	1.0656	0.26	0.5280	0.55	3.2736
0.002	0.41	1.0032	0.59	1.8480	0.44	1.1424	0.30	0.4512	0.78	2.7696
0.004	0.55	0.8352	0.98	1.8672	0.62	1.0008	0.37	0.4008	1.14	2.2344
0.006	0.77	0.8976	1.34	1.8176	0.79	0.9408	0.44	0.3808	1.48	2.0432
0.008	0.98	0.9336	1.75	1.8552	0.98	0.9336	0.52	0.3828	1.84	1.9632
0.010	1.23	0.9850	2.09	1.8106	1.13	0.8890	0.61	0.3850	2.15	1.8722
0.020	2.09	0.9053	3.63	1.6445	2.16	0.9389	0.83	0.3010	3.21	1.4429
0.040	3.51	0.7934	6.24	1.4486	3.60	0.8150	1.12	0.2198	4.22	0.9638
0.060	4.62	0.7066	9.09	1.4218	4.74	0.7258	1.32	0.1786	5.96	0.9210
0.080	5.72	0.6619	11.13	1.3111	4.98	0.5731	1.56	0.1627	7.31	0.8527
0.100	6.41	0.5958	13.44	1.2707	5.30	0.4892	1.77	0.1503	9.22	0.8655

Table 3.3.2: The Conductance (*k*) and equivalent conductance (λ_C) of Dihydropyrimidines in DMSO at 298.15 K.

Conc. M	$k.10^5$ mho	λ_C $mho.cm^2.equi.^{-1}$	$k.10^5$ mho	λ_C $mho.cm^2.equi.^{-1}$	$k.10^5$ mho	λ_C $mho.cm^2.equi.^{-1}$	$k.10^5$ mho	λ_C $mho.cm^2.equi.^{-1}$	$k.10^5$ mho	λ_C $mho.cm^2.equi.^{-1}$
	RVG-1		***RVG-2***		***RVG-3***		***RVG-4***		***RVG-5***	
0.000	0.016	-	0.016	-	0.016	-	0.016	-	0.016	-
0.001	0.134	1.0848	0.124	0.9888	0.191	1.6320	0.117	0.9216	0.291	2.5920
0.002	0.237	1.0368	0.177	0.7488	0.286	1.2720	0.197	0.8448	0.524	2.4144
0.004	0.425	0.9696	0.288	0.6408	0.497	1.1424	0.382	0.8664	0.980	2.3016
0.006	0.652	1.0096	0.375	0.5664	0.678	1.0512	0.548	0.8432	1.350	2.1264
0.008	0.871	1.0200	0.473	0.5424	0.870	1.0188	0.760	0.8868	1.670	1.9788
0.010	1.010	0.9494	0.520	0.4790	1.070	1.0070	1.020	0.9590	2.040	1.9382
0.020	1.560	0.7387	0.770	0.3595	1.750	0.8299	1.680	0.7963	3.570	1.7035
0.040	2.700	0.6430	1.320	0.3118	3.070	0.7318	3.020	0.7198	3.780	0.9022
0.060	3.770	0.5998	1.780	0.2814	4.080	0.6494	4.160	0.6622	4.070	0.6478
0.080	5.370	0.6419	2.260	0.2687	5.010	0.5987	5.340	0.6383	4.530	0.5411
0.100	6.330	0.6057	2.890	0.2754	5.910	0.5653	6.810	0.6517	4.680	0.4473
	RVG-6		***RVG-7***		***RVG-8***		***RVG-9***		***RVG-10***	
0.001	0.027	0.0525	0.023	0.0172	0.022	0.0077	0.030	0.0740	0.023	0.0163
0.002	0.038	0.0748	0.028	0.0301	0.029	0.0335	0.045	0.1036	0.027	0.0262
0.004	0.060	0.0830	0.036	0.0316	0.039	0.0385	0.084	0.1361	0.039	0.0378
0.006	0.082	0.0867	0.045	0.0337	0.050	0.0421	0.121	0.1436	0.051	0.0423
0.008	0.104	0.0888	0.053	0.0345	0.062	0.0441	0.154	0.1433	0.061	0.0429
0.010	0.124	0.0886	0.159	0.1187	0.078	0.0490	0.214	0.1660	0.110	0.0765
0.020	0.356	0.1441	0.243	0.0955	0.137	0.0499	0.282	0.1122	0.192	0.0735
0.040	0.567	0.1174	0.385	0.0783	0.248	0.0488	0.371	0.0753	0.301	0.0602
0.060	0.785	0.1095	0.554	0.0764	0.361	0.0487	0.497	0.0682	0.438	0.0598
0.080	0.883	0.0927	0.718	0.0749	0.451	0.0462	0.620	0.0644	0.562	0.0582
0.100	0.996	0.0839	0.910	0.0765	0.522	0.0431	0.801	0.0671	0.756	0.0632

Figure 3.3.1: The variation of Conductance with concentration for Dihydropyrimidines in DMF at 298.15 K.



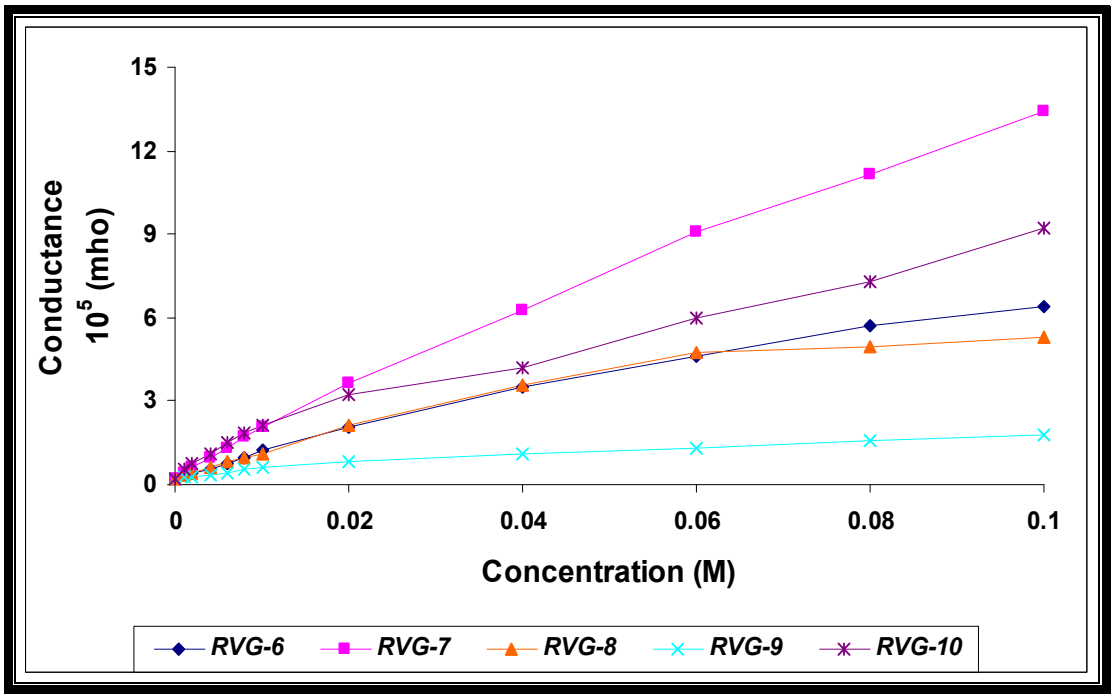
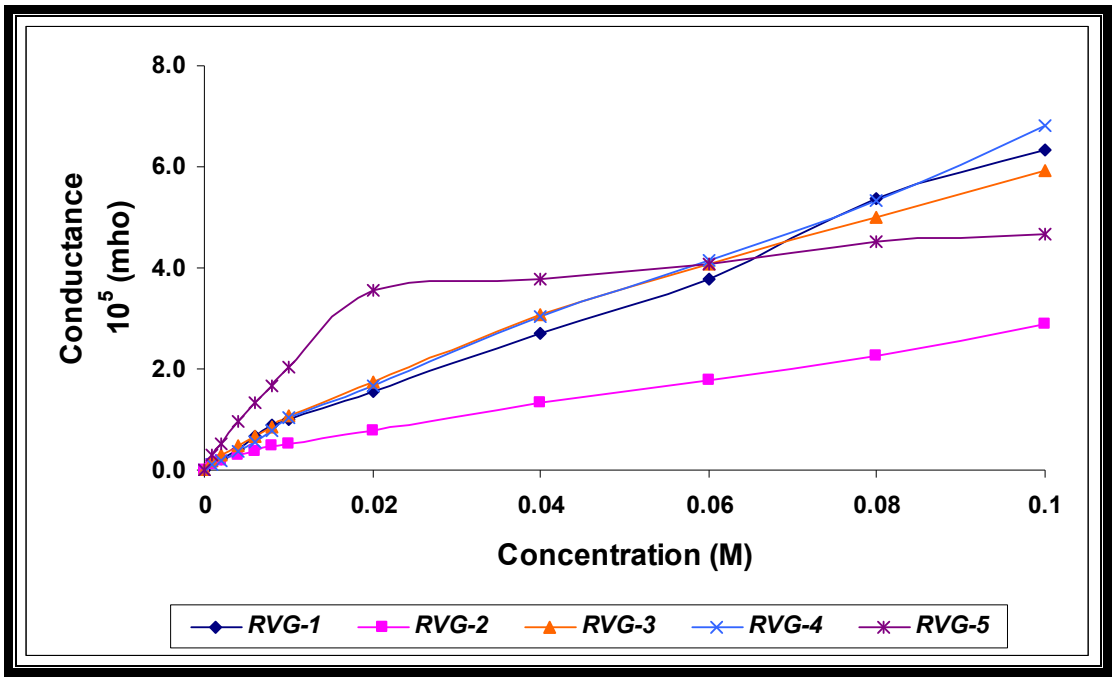


Figure 3.3.2: The variation of Conductance with concentration for Dihydropyrimidines in DMSO at 298.15 K.



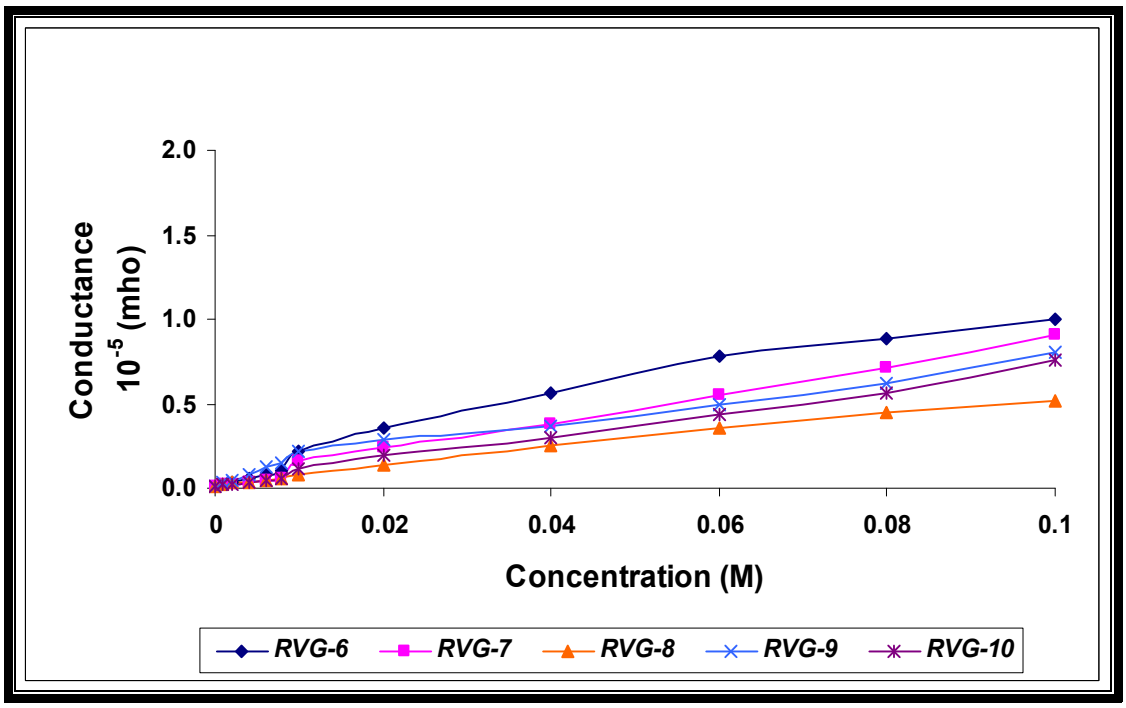
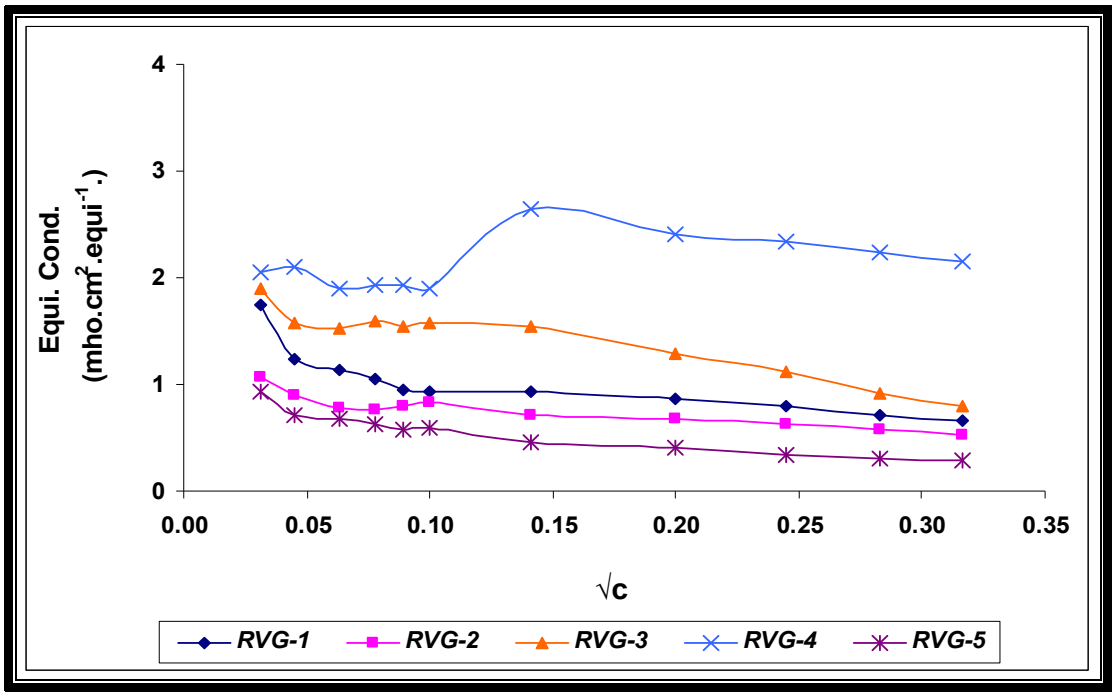


Figure 3.3.3: The variation of equivalent conductance with √C for Dihydropyrimidines in DMF at 298.15 K.



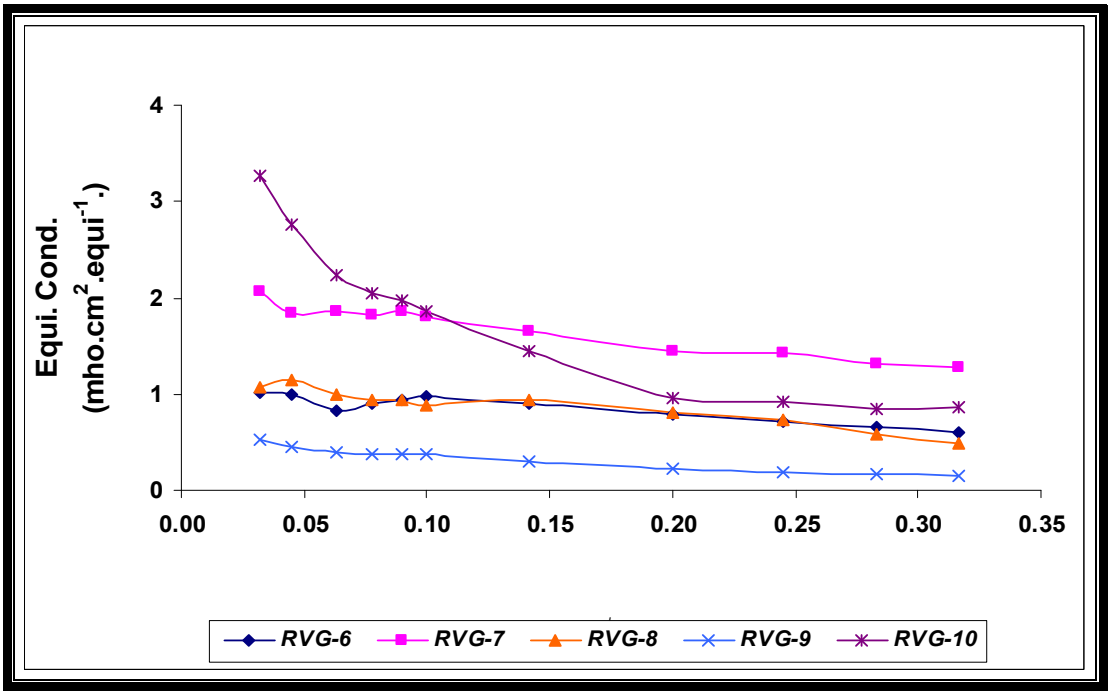
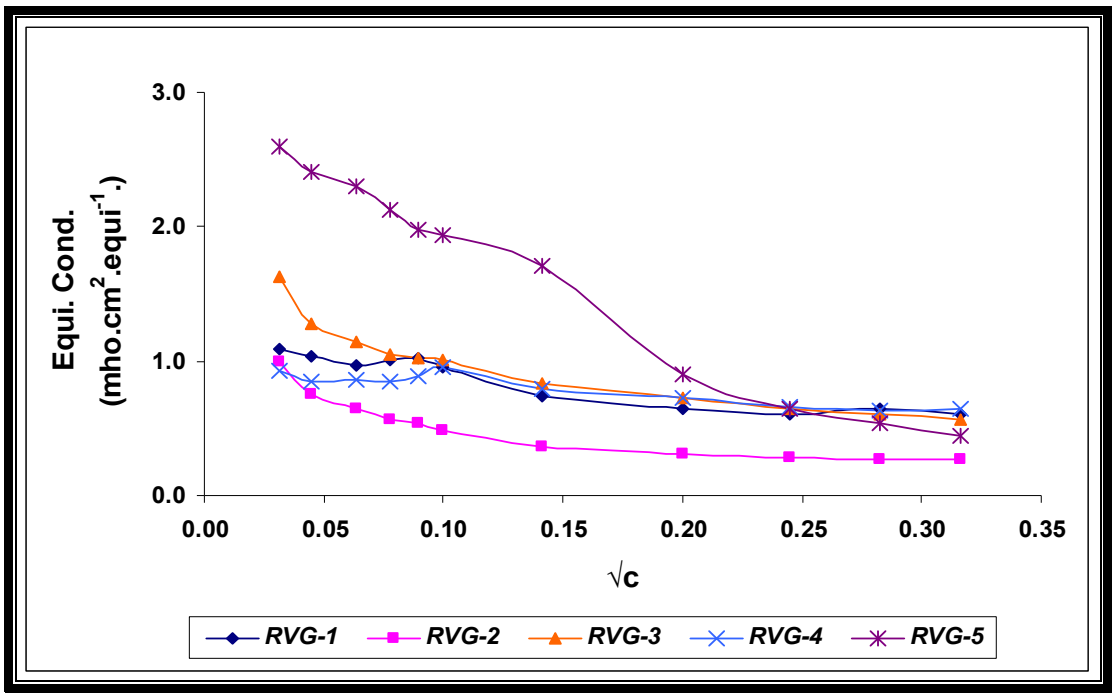
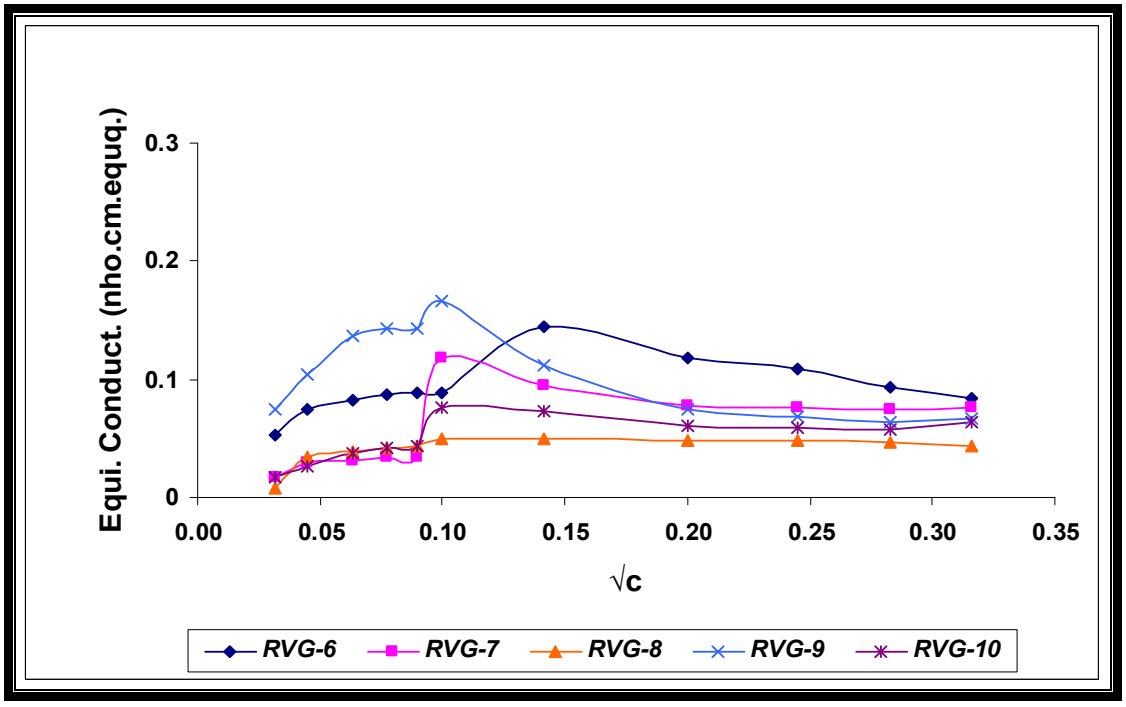


Figure 3.3.4: The variation of equivalent conductance with √C for Dihydropyrimidines in DMSO at 298.15 K.





$$k = k_0 + \lambda_0 c + c\phi_{(c)} \qquad \text{..... (3.3.3)}$$

where k and k_0 are the electrolytic conductivity of the solutions and solvent respectively. c is the equivalent concentration and the function $\Phi_{(c)}$ denotes the effect of interionic interactions. The limiting conductivity can be determined accurately from the slope, dk/dc of plot of k verses c, provided other derivatives (dk_0/dc) and $d[c\Phi_{(c)}]/dc$ in differential form of equation (3.3.3) are neglected as compared to λ_0, which can be determined from differential form of equation (3.3.3) is

$$\frac{dk}{dc} = \frac{dk_0}{dc} + \lambda_0 + \frac{d\left[c\phi_{(c)}\right]}{dc} \qquad \text{..... (3.3.4)}$$

Table 3.3.3 shows the λ_0 values for all studied compounds along with those determined by extrapolation. For the system where λ_c decreases at low concentrations, λ_0 could not be evaluated. Comparison of λ_0 values in Table 3.3.5 show that for most of the systems, values are in good agreement. However, for some cases, deviations are significant suggesting thereby that equations (3.3.3) and (3.3.4) are not valid for these systems. The reason for the deviation may be due to the fact that in equation (3.3.3), the term for interionic interactions[37] i.e., are neglected, which are actually present in the studied solutions, as discussed in section 1 (acoustical properties).

Table 3.3.3: The limiting equivalent conductance (λ_0) of all the compounds in DMF and DMSO at 298.15 K.

Compound Code	λ_0 $mho.cm^2.equi.^{-1}$ from graph	$\lambda_0 10^3$ $mho.cm^2.equi.^{-1}$ from eq. (3.3.4)	λ_0 $mho.cm^2.equi.^{-1}$ from graph	$\lambda_0 10^3$ $mho.cm^2.equi.^{-1}$ from eq. (3.3.4)
	DMF		*DMSO*	
RVG -1	1.10	0.94	1.10	1.01
RVG -2	1.14	0.83	0.83	0.49
RVG -3	2.01	1.59	1.10	1.01
RVG -4	-	1.98	0.86	0.97
RVG -5	0.80	0.59	2.56	2.1
RVG -6	1.13	1.00	-	0.108
RVG -7	1.95	1.89	-	0.045
RVG -8	1.12	0.92	-	0.060
RVG -9	0.68	0.39	-	0.193
RVG -10	2.42	2.01	-	0.056

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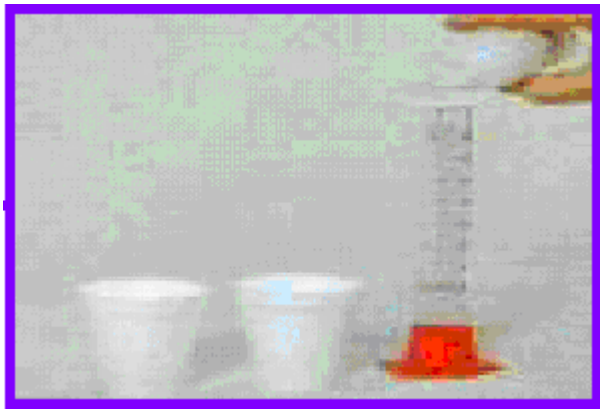


Section-IV

Solubility

INTRODUCTION

The extensive information on the thermodynamic properties of organic compounds is needed not only their use in many industrial processes but also for the advancement of theoretical developments through an understanding of the intermolecular forces in solution for structure-property relationship. Solubility data is important information in drug discovery, drug formulation and crystallization-based separation investigations.

The solubility of drug is essential information in drug discovery and is important in the preparation of liquid drug formulation stages in the pharmaceutical industry[1, 2]. There are many methods for solubilization of drugs including cosolvency, surface active agents, salt information, complexation, hydrotropism, crystal engineering and preparation of soluble prodrug[3-5].

The process of dissolving is a process which involves the breaking and making of bonds and that involves energy which is in the form of heat.

Thus, the process of dissolution is accompanied by the heat change i.e., enthalpy change (ΔH_{sol}). If the heat is absorbed, the process is called endothermic. In this case, ΔH_{sol} is positive. If the heat is evolved i.e., process is exothermic and the ΔH_{sol} values will be negative.

This enthalpy change is known as heat of solution, which is the change in heat content when one mole of substance is dissolved in specific quantity of solvent at a given temperature.

The molar heat of solution and melting temperature of a substance can be determined from the solubility measurements[6]. In recent years many researchers have been worked on solubility of some natural compounds[7, 8], some organic[9-11], polymers[12, 13], amino acids[14, 15], drugs[16-19], vitamins[20], ionic liquids[21, 22], and inorganic compounds[23-25] by various methods[26-33]. In our laboratory, heat of solution of some synthesized heterocyclic compounds and drugs has also been determined[34-36]. From the solubility data, some thermodynamic parameters have also been evaluated.

In the present work, the solubility for some dihydropyrimidinones derivatives was determined in N, N-dimethylformamide (DMF) and dimethylsulfoxide (DMSO) at different temperatures (298.15 to 318.15) K. Further, some thermodynamic parameters such as enthalpy, Gibb's free energy and entropy of different solutions have also been evaluated from the solubility data.

EXPERIMENTAL

The heat of solution of dihydropyrimidines has been studied in DMF and DMSO. These solvents were purified and fractionally distilled prior to use by the method reported in the literature[37].

The solubilities were measured by a gravimetric method[38]. For each measurement, an excess mass of dihydropyrimidinone was added to a known mass of solvent. Then, the equilibrium cell was heated to a constant temperature with continuous stirring. After, at least 3 h (the temperature of the water bath approached constant value, then the actual value of the temperature was recorded), the stirring was stopped and the solution was kept still for 2 h. A portion of this solution was filtered and by a preheated injector, 2 ml of this clear solution was taken in another weighted measuring vial (m_0). The vial was quickly and tightly closed and weighted (m_1) to determine the mass of the sample (m_1- m_0). Then, the vial was covered with a piece of filter paper to prevent dust contamination. Then, the vial was placed in at room temperature to evaporate the solvent. After the solvent in the vial had completely evaporated, the vial was dried and reweighed (m_2) to determine the mass of the constant residue solid (m_2- m_0). All the weights were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an accuracy of ± 0.0001 g. Thus, the solid concentration of the sample solution of mole fraction, *x*, could be determined from equation 1.

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \qquad .. (3.4.1)$$

where M_1 is the molar mass of dihydropyrimidinone and M_2 is the molar mass of the solvent.

RESULTS AND DISCUSSION

The solubility *(x)* of synthesized compounds in the studied solvents is given in Tables 3.4.1 and 3.4.2. It is evident from these Tables that the solubility increases with temperature in both the solvents. Figure 3.4.1 shows the variation of mole fraction solubility (x) against temperature for RVG-1 in DMF and DMSO. Comparison of solubility of these compounds in DMF and DMSO shows that overall solubility is greater in DMF than that in DMSO. The dielectric constant and dipole moment of DMF (36.71, 3.86) are greater than that of DMSO (46.6, 3.9). Thus, these properties of solvent play an important role on the solubility, as expected.

The temperature dependence solubility in solvents is described by the modified Apelblat equation[39, 40]

$$\ln x = A + B/(T/K) \qquad \text{... (3.4.1)}$$

where x is the mass fraction solubility of compounds; T is the absolute temperature and A, and B are the coefficients. The values of these coefficients are given in Table 3.4.3. Using these values of A and B, calculated solubilities x_c were evaluated and are reported in Tables 3.4.1 and 3.4.2.

The relative deviations *(RD)* between the experimental and calculated values of solubilities are also calculated by equation 3.4.2 and are given in Tables 3.4.1 and 3.4.2.

$$\textit{Relative Deviation} = \left(\frac{x - x_c}{x} \right) \qquad \text{..... (3.4.2)}$$

Further, relative average deviations *(ARD)* and root-mean-square deviations *(rmsd)* were calculated by equations 3.4.3 and 3.4.4 and are listed in Tables 3.4.5 and 3.4.6.

$$ARD = \frac{1}{N} \sum_{i}^{N} \left(\frac{x_i - x_c}{x_i} \right) \qquad \text{..... (3.4.3)}$$

$$rmsd = \left[\sum_{i=1}^{N} \frac{(x_{ci} - x_i)^2}{N-1} \right]^{1/2} \quad \text{..... (3.4.4)}$$

where *N* is the number of experimental points.

Table 3.4.1: The experimental solubility *(x),* calculated solubility *(x_c)* and relative deviation *(RD)* of Dihydropyrimidinones in DMF at different temperatures.

Temp. K	*x. 10^2*	*$x_c.10^2$*	*100 RD*	*x. 10^2*	*$x_c.10^2$*	*100 RD*
	RVG-1			***RVG-6***		
298.15	2.3942	2.4144	-0.8458	2.5976	2.6249	-1.0504
303.15	2.6012	2.5817	0.7047	2.9504	2.8821	2.3022
308.15	2.8144	2.7605	1.9148	3.3087	3.1645	4.3570
313.15	2.9711	2.9518	0.6128	3.5513	3.4746	2.1238
318.15	3.1325	3.1563	-0.7603	3.7837	3.8151	-0.8288
	RVG-2			***RVG-7***		
298.15	2.0191	2.0246	-0.2766	2.3994	2.4983	-4.1223
303.15	2.2218	2.2465	-1.1938	2.8305	2.8154	0.5165
308.15	2.4283	2.4927	-2.6490	3.2556	3.1727	2.5475
313.15	2.7426	2.7658	-0.9423	3.5743	3.5753	-0.1491
318.15	3.0545	3.0689	-0.4727	3.8799	4.0291	-3.8439
	RVG-3			***RVG-8***		
298.15	3.0658	3.1884	-3.9961	2.7580	2.8242	-2.4018
303.15	3.4312	3.4212	0.2564	3.0324	3.0502	-0.6669
308.15	3.7873	3.6711	3.0691	3.3096	3.2943	0.4628
313.15	3.9324	3.9392	-0.2331	3.5325	3.5579	-0.7915
318.15	4.0719	4.2268	-3.8062	3.7518	3.8427	-2.4220
	RVG-4			***RVG-9***		
298.15	3.2160	3.1933	0.7077	2.8882	2.8844	0.1294
303.15	3.5228	3.5114	0.2434	3.1615	3.2005	-1.2028
308.15	3.8182	3.8613	-1.1290	3.4357	3.5512	-3.3619
313.15	4.2631	4.2461	0.3274	3.9025	3.9404	-1.0350
318.15	4.7017	4.6691	0.6930	4.3692	4.3721	-0.0681

	RVG-5			***RVG-10***		
298.15	2.4148	2.3842	1.2646	3.0024	2.9135	2.9635
303.15	2.6904	2.6561	1.2597	3.2716	3.2343	1.0907
308.15	2.9593	2.9590	0.0114	3.5355	3.5905	-1.5564
313.15	3.3421	3.2964	1.3060	4.0513	3.9860	1.5805
318.15	3.7220	3.6723	1.3365	4.5547	4.4250	2.8476

Table 3.4.2: The experimental solubility *(x),* calculated solubility *(x_c)* and relative deviation *(RD)* of Dihydropyrimidinones in DMSO at different temperatures.

Temp. K	***x. 10^2***	***x_c.10^2***	***100 RD***	***x. 10^2***	***x_c.10^2***	***100 RD***
	RVG-1			***RVG-6***		
298.15	2.2628	2.2440	0.8274	2.0230	2.0159	0.3471
303.15	2.3440	2.3216	0.5293	2.1122	2.0784	1.5994
308.15	2.4262	2.4019	1.0019	2.2013	2.1427	2.6623
313.15	2.5095	2.4850	0.9760	2.2285	2.2091	0.8727
318.15	2.5937	2.5709	0.8793	2.2957	2.2775	0.7942
	RVG-2			***RVG-7***		
298.15	2.2130	2.2481	-1.5850	1.9252	1.9241	0.0595
303.15	2.2867	2.2958	-0.3961	2.0087	1.9797	1.4445
308.15	2.2805	2.3445	-2.8086	2.0422	2.0369	0.2586
313.15	2.3589	2.3943	-1.4980	2.1093	2.0958	0.6404
318.15	2.4174	2.4451	-1.1454	2.1694	2.1563	0.6030
	RVG-3			***RVG-8***		
298.15	2.1397	2.1818	-1.9633	2.0242	2.0346	-0.5148
303.15	2.2548	2.2685	-0.6080	2.0901	2.1060	-0.7603
308.15	2.2699	2.3587	-3.9145	2.1661	2.1799	-0.6404
313.15	2.3984	2.4525	-2.2550	2.2394	2.2564	-0.7623
318.15	2.5185	2.5500	-1.2532	2.3227	2.3356	-0.5575
	RVG-4			***RVG-9***		
298.15	2.5097	2.4869	0.9096	2.1708	2.1619	0.4112
303.15	2.5813	2.5460	1.3666	2.2611	2.2378	1.0308
308.15	2.6329	2.6066	09997	2.3214	2.3163	0.2174
313.15	2.6902	2.6685	0.8055	2.4119	2.3976	0.5928
318.15	2.7675	2.7320	1.2842	2.4986	2.4818	0.6727

	RVG-5			RVG-10		
298.15	2.1226	2.1778	-2.6028	2.2280	2.2455	-0.7820
303.15	2.2540	2.2498	0.1858	2.2978	2.3185	-0.8990
308.15	2.3853	2.3241	2.5673	2.3782	2.3938	-0.6567
313.15	2.4012	2.4008	0.0147	2.4663	2.4717	-0.2192
318.15	2.4171	2.4801	-2.6088	2.5123	2.5520	-1.5813

Table 3.4.3: Coefficient *A* and *B* of equation 3.4.1, Relative Average Deviation *(ARD)*, and root Mean Square Deviation *(rmsd)* of Dihydropyrimidinones in DMF and DMSO.

Compounds	*A*	*B*	10^7 *rmsd*	*100 ARD*
		DMF		
RVG-1	-7.71	0.0134	0.36	0.32
RVG-2	-10.10	0.0208	0.45	-1.10
RVG-3	-7.65	0.0141	4.21	-0.94
RVG-4	-9.10	0.0190	0.29	0.16
RVG-5	-10.17	0.0216	0.51	1.03
RVG-6	-9.21	0.0187	2.62	1.38
RVG-7	-10.81	0.0239	3.13	-1.01
RVG-8	-8.15	0.0154	1.12	-1.16
RVG-9	-9.74	0.0208	1.33	-1.12
RVG-10	-9.76	0.0209	2.65	1.38
		DMSO		
RVG-1	-5.82	0.0068	0.17	0.84
RVG-2	-5.05	0.0042	0.59	-1.48
RVG-3	-6.15	0.0078	1.10	-1.99
RVG-4	-5.09	0.0047	0.33	1.07
RVG-5	-5.76	0.0065	0.86	-0.48
RVG-6	-5.72	0.0061	0.42	1.25
RVG-7	-5.65	0.0057	0.09	0.60
RVG-8	-5.95	0.0069	0.08	-0.64
RVG-9	-5.89	0.0069	0.09	0.58
RVG-10	-5.70	0.0064	0.20	-0.82

These values suggest that there is good agreement between experimental and calculated solubility values. So, the modified Apelblat equation can be used as model for the evaluation of solubility of these compounds in different solvents.

According to van't Hoff analysis, the standard enthalpy change of solution is obtained from the slope the *ln x* versus *1/T* plot. However, in recent thermodynamic treatments, some modifications have been introduced in the van't Hoff equation to diminish the propagation of errors and consequently to separate the chemical effects from those due to statistical treatment used when enthalpy-entropy compensation plots are developed[41]. For this reason, the mean harmonic temperature (T_{hm}) is used in the van't Hoff analysis, which is calculated by the following equation.

$$T_{hm} = \frac{n}{\sum_{i}^{n}\left(1/T\right)} \qquad \text{..... (3.4.5)}$$

where *n* is the number of temperatures studied and *T* is absolute temperature of the experiment. In the present case, the T_{hm} value obtained is 308 K.

So, the modified van't Hoff equation is[42, 43].

$$\frac{\partial \ln x}{\partial\left(1/T - 1/T_{hm}\right)_P} = -\frac{\Delta H_{sol}}{R} \qquad \text{..... (3.4.6)}$$

where ΔH_{sol} is the heat of solution and *R* is the gas constant.

Figure 3.4.2 shows the van't Hoff plots for RVG-1 in DMF and DMSO solutions. The slope of these linear plots gives the values of ΔH_{sol} whereas Gibb's free energy of dissolution (ΔG_{sol}) was evaluated from the intercept using the following equation[42].

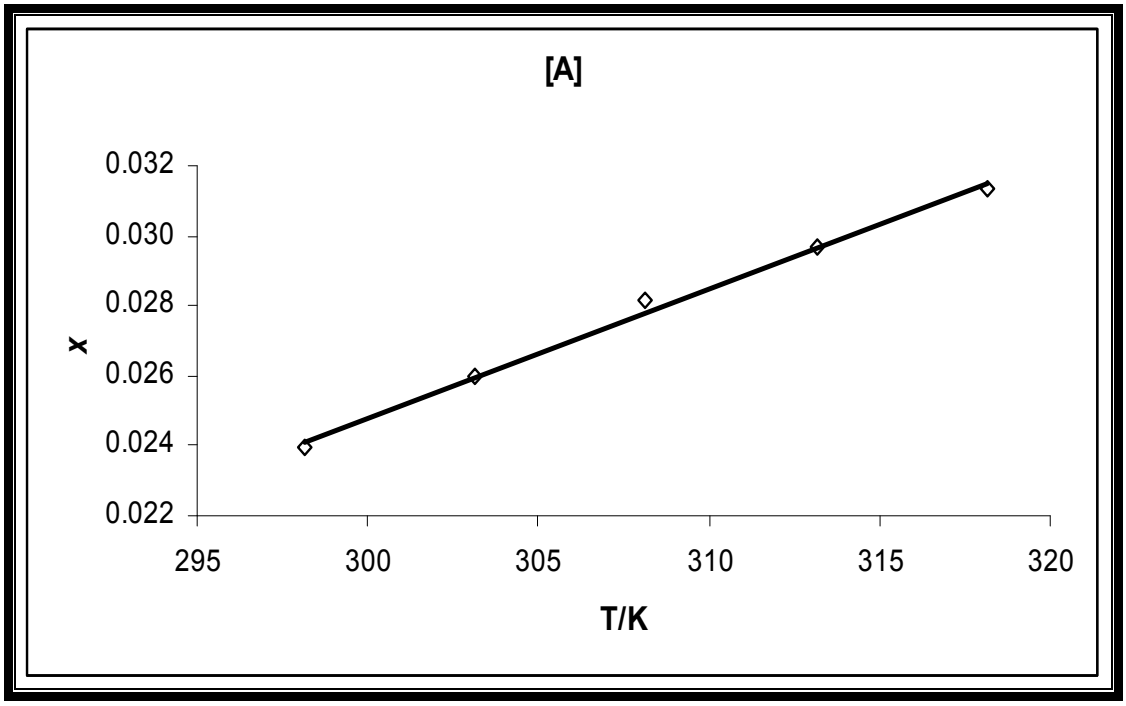
$$\Delta G_{sol} = -RT_{hm}.\ intercept \qquad \text{..... (3.4.7)}$$

Using these evaluated ΔH_{sol} and ΔG_{sol} values, the entropies of solutions ΔS_{sol} were obtained from equation[44] 3.4.8

$$\Delta S_{sol} = \frac{\Delta H_{sol} - \Delta G_{sol}}{T_{hm}} \qquad \text{….. (3.4.8)}$$

All these thermodynamic parameters are given in Tables 3.4.4.

Figure 3.4.1: The mole fraction solubility (x) against temperature (T/K) for RVG-1 in DMF (A) and DMSO (B).



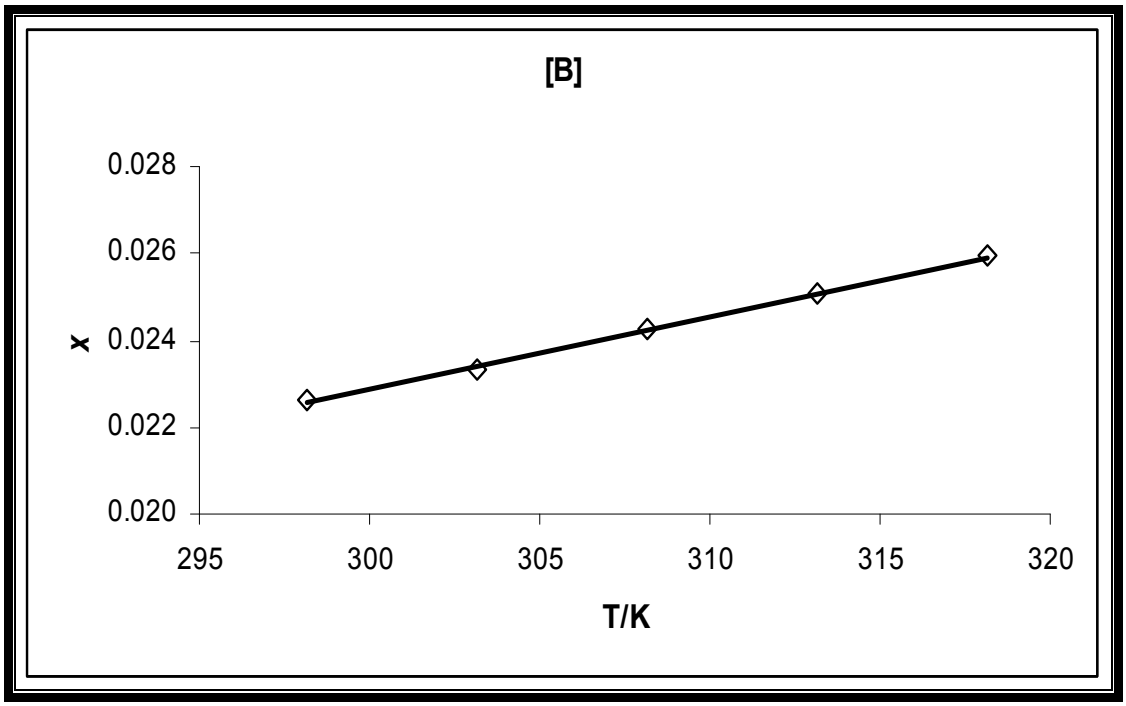
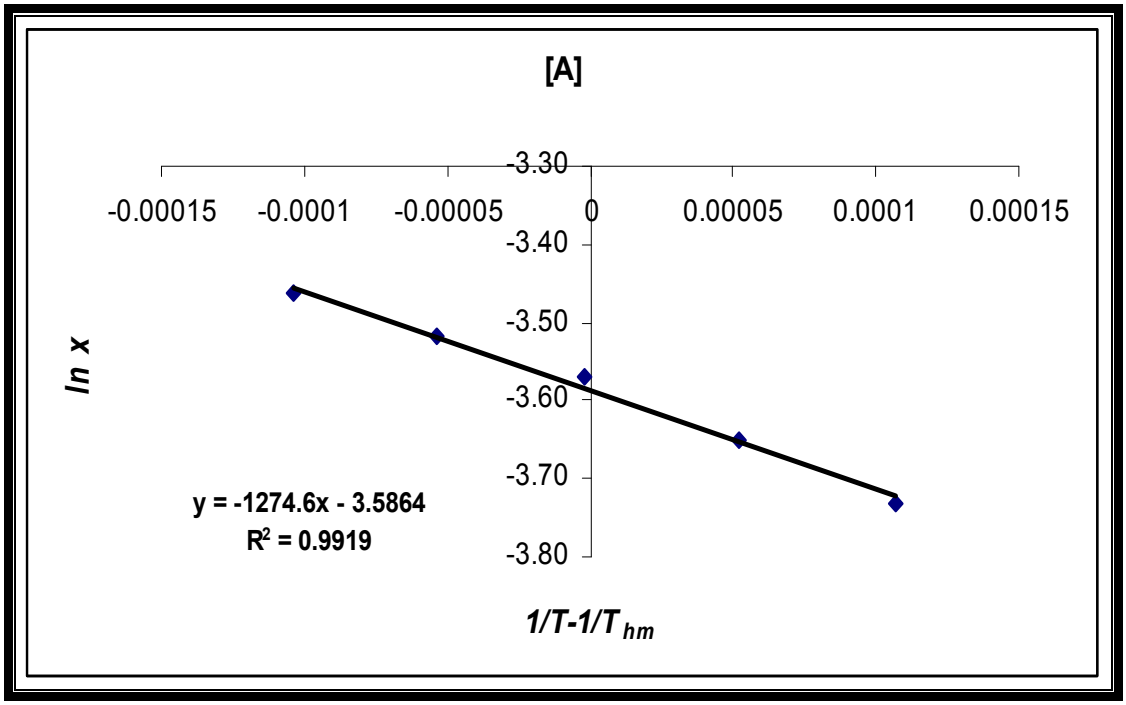


Figure 3.4.2: van't Hoff plots for for RVG-1 in [A] DMF and [B] DMSO.



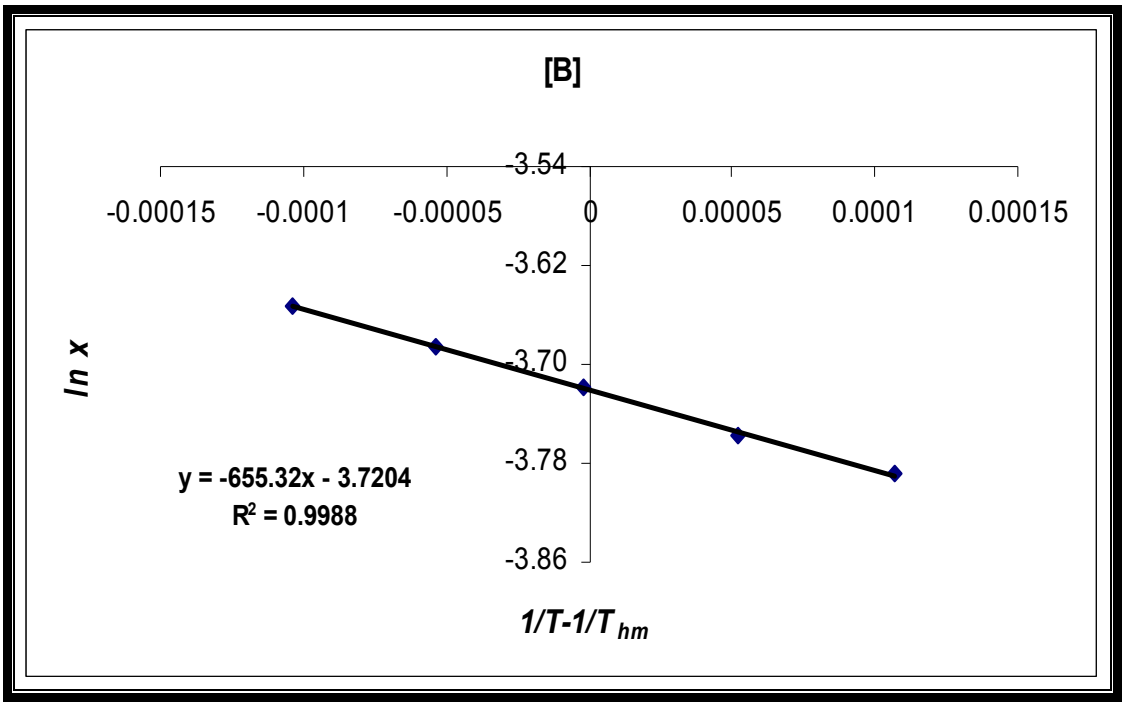


Table 3.4.4: The thermodynamic function of Dihydropyrimidinones in DMF and DMSO at 308 K *(T_{hm}).*

Compound code	*ΔH_{sol} kcal.mol^{-1}*	*ΔG_{sol} kcal.mol^{-1}*	*ΔS_{sol} cal.mol^{-1}.K^{-1}*	*ΔH_{sol} kcal.mol^{-1}*	*ΔG_{sol} kcal.mol^{-1}*	*ΔS_{sol} cal.mol^{-1}.K^{-1}*
	DMF			*DMSO*		
RVG-1	2.53	2.19	1.09	1.28	2.27	-3.22
RVG-2	3.90	2.26	5.33	0.78	2.30	-4.93
RVG-3	2.66	2.02	2.06	1.46	2.30	-2.72
RVG-4	3.57	1.99	5.15	0.89	2.22	-4.32
RVG-5	4.07	2.14	6.25	1.22	2.30	-3.49
RVG-6	3.54	2.10	4.67	1.15	2.34	-3.84
RVG-7	4.51	2.11	7.77	1.07	2.38	-4.24
RVG-8	2.90	2.09	2.61	1.29	2.34	-3.40
RVG-9	3.90	2.04	6.03	1.30	2.30	-3.24
RVG-10	3.94	2.02	6.21	1.20	2.28	-3.50

It is evident from Table 3.4.4 that for all the compounds ΔH_{sol} and ΔG_{sol} values are positive whereas ΔS_{sol} values are negative for DMSO and positive values for DMF. When stronger bonds are broken and weaker bonds are formed, energy is consumed and so, ΔH_{sol} becomes positive[44]. This indicates endothermic dissolution of compounds where the enthalpy term contributes to an unfavorable positive value of ΔG_{sol} [44].

Thus, positive values of ΔG_{sol} indicates that the dissolution process is not spontaneous[44, 45].

The negative value of entropy indicates less randomness in solutions[44].

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Section-V

Thermal Properties

INTRODUCTION

Studies on thermal properties of substances are of great importance from both scientific and practical of view. Scientific and technological achievements together with demands based on industrial requirement have permitted the development of various types of materials that can withstand at much higher temperatures and more corrosive environments.

Various techniques have been developed for the measurement of thermal properties. Some of the most commonly used techniques are Differential Scanning Calorimetry (DSC), Differential Thermal Analysis (DTA), Thermo Gravimetric Analysis (TGA), Evolved Gas Detection (EGD), Evolved Gas Analysis (EGA) etc. In the present study, thermal analysis is done by DSC and TGA techniques.

Thermogravimatric analysis covers a wide spectrum of thermoanalytical techniques, which monitor one or more physical properties of a substance that is undergoing a temperature programmed heating as a function of time or temperature. This technique is widely used in the fields of gas-solid interactions, fuels, catalysis, polymer and chemical synthesis. This method can not distinguish the actual nature of the material evolved in the course of the process and is also handicapped in resolving overlapped thermal events.

This technique has been used in analyzing and characterizing wide variety of materials like coals, rocks and minerals[1], petroleum coke[2], rubber and styrene butadiene blends[3], hydrocarbon sludge from petrochemical plants[4], polyimide resins[5], superconducting materials[6], hydrogen storage materials[7], and even rocks from moon.

Apart from its traditional use in investigations of chemical reactions, temperature programmed decompositions, study of reaction kinetics and mechanism, determination of material purity etc., this technique is also used in the areas of forensic science[8], archeology[9, 10], catalysis[11, 12], polymers[13-17], nanotubes[18, 19,] and pharmaceuticals[20-25].

One of the most important applications of thermo gravimetry is to determine thermal stability of polymer and binding materials. Houriez and co-workers[26] have reported the thermal analysis of polymer dispersed liquid crystal by using photo pyroelectric technique. Kurt and Trilogica[27] have

reported the quality assurance of polymer and plastic by thermal analysis and differential scanning calorimetry. The thermal study of honey[28], tobacco[29] and edible oil[30] has also been reported. Bei et al.[31] have reported the thermal decomposition kinetic of 5-flourouracil from thermogravimetric analysis.

The decomposition temperature, adsorption and desorption phenomena, ash content, flame retardancy, rates of evaporation or sublimation can also be determined by TGA[32]. The information from TGA can be used to compliment differential scanning calorimetry (DSC) data. Some instruments are equipped to acquire both DSC and TGA data simultaneously. In this case, the DSC data provides the thermodynamic account of different chemical and physical reactions occurring and the TGA data provides an account of any mass changes that are coupled to the reactions. TGA method is useful for plant engineers in designing safe and economical plant and process for the manufacture of various chemicals.

DSC is a versatile thermal technique used to provide quantitative and qualitative information about physical and chemical changes involving endothermic or exothermic processes or heat capacity changes. It also provides useful information about crystallinity, stability of crystallites, glass transition temperature, cross-linking and heat of polymerization etc.

Literature survey shows that several investigations have been carried out on the application of thermal methods in pharmaceutical industry. Mamede et al.[33] have reported thermal behavior of some pharmaceuticals and drugs. Bogdan and co-workers[34] have reported the thermal stability and kinetic decomposition of diclofenac sodium. Lapuerta and co-workers[35] have reported the thermogravimetric analysis of diesel particulate matter. Wu and Hung[36] have done the thermal analysis of thin films of 1,4-phenylene-cis-benzobisoxazole or PBO. Thermal studies of some organic and inorganic compounds have also been studied[37-45]. However, little work has been done of thermal analysis of pyrimidine moiety[46-48].

In the present study, thermal properties of some new synthesized dihydropydimidinones have been studied by DSC and TGA techniques. Using thermograms, various kinetic parameters have also been evaluated.

THEORY

From TGA curves, various kinetic parameters can be evaluated by several methods. In all these methods, it is assumed that thermal and diffusion barriers are negligible because small quantity of material is used. The shape of any TGA curve depends on the nature of apparatus and the way in which it is used. Further, Arrhenius equation is valid in all these methods.

The kinetic treatments are generally based on the relationship of the type:

$$dC/dt = K f(C) \quad \text{... (3.5.1)}$$

where C is the degree of conversion, t is time and K is rate constant. $f(C)$ is a temperature independent function of C.

The constant K is assumed to have the Arrhenius form:

$$K = A\, e^{-E/RT} \quad \text{... (3.5.2)}$$

C can also be defined as:

$$C = 1-(W/W_0) \quad \text{... (3.5.3)}$$

where W_0 and W are the initial weight at $t=0$ and weight at any time t of the material.

Equation (3.5.3) can be written as:

$$(W/W_0) = (1-C) \quad \text{... (3.5.4)}$$

W/W_0 is known as residual weight fraction.

Thus, the rate of conversion is,

$$dC/dt = -(1/W_0)(dW/dt) \quad \text{... (3.5.5)}$$

For homogeneous kinetics, the conversion is assumed to be of the form:

$$f(C) = (1-C)^n \quad \text{... (3.5.6)}$$

where n is the order of the reaction.

Substituting the values from equation (3.5.2) and (3.5.6) in equation (3.5.1) gives:

$$dC/dt = A\, e^{-E/RT} (1-C)^n$$

or $$dC/dt = (A/\beta)\, e^{-E/RT} (1-C)^n \quad \text{... (3.5.7)}$$

where A is the frequency factor, β is the rate of heating and E is the energy of activation.

Various methods for single and multiple heating rates have been reported. The methods of single heating rate are as follows:

1. Freeman-Carroll[49] and Anderson-Freeman Method[50]:

At a single heating rate, Freeman and Carroll gave the following relation to analysis TGA data:

$$\ln (dC/dt)/\ln (1-C) = n - E/R\, [(1/T)/(\Delta \ln(1-C)] \quad \text{... (3.5.8)}$$

A plot of left hand side against $(1/T)/(\Delta \ln(1-C))$ gives a straight line with a slope equal to $-E/R$ and the intercept is equal to n.

Anderson and Freeman then derived the following equation by using equation (3.5.8):

$$(\Delta \ln[dC/dt]) = n\, (\Delta \ln(1-C)) - E/R\, \Delta(1/T) \quad \text{... (3.5.9)}$$

The plot of $(\Delta \ln[dC/dt])$ against $(\Delta \ln(1-C))$ for equal intervals of $\Delta(1/T)$ gives a straight line with slope equal to n and intercept $-E/R\Delta(1/T)$.

2. Sharp-Wentworth method[51]:

To analyse the TGA data for first order kinetics (n=1), Sharp and Wentworth gave the relation:

$$\log [(dC/dt)/(1-C)] = \log (A/\beta) - (E/2.303R).(1/T) \quad \text{... (3.5.10)}$$

The plot of $\log [(dC/dt)/(1-C)]$ against $1/T$ would be a straight line with slope equal to $-(E/2.303R)$ and intercept equal to $\log (A/\beta)$.

3. Chatterjee Method[52]:

Based on the weight units, the following relation was developed by Chatterjee:

$$n = [\log(dW/dt)_1 - \log(dW/dt)_2] / (\log W_1 - \log W_2) \quad \text{... (3.5.11)}$$

where W_1 and W_2 are the sample weights.

4. Horowitz and Metzger method[53]:

In this method, the value of energy of activation E can be determined from a single TG curve by the relation:

$$ln\,[ln(1-C)^{-1}] = (E/RT_s^2)\theta \quad \text{... (3.5.12)}$$

where $\theta = T-T_s$. T_s is the temperature at which the rate of decomposition is maximum. The frequency factor A and entropy change ΔS can be determined by the following equations:

$$ln\,E - ln\,(RT_s^2) = ln\,A - ln\beta - E/RT_s \quad \text{... (3.5.13)}$$

$$A = (k_bT / h)\, e^{\Delta S/R} \quad \text{... (3.5.14)}$$

where k_b is Boltzmann constant and h is Planck's constant.

EXPERIMENTAL

Thermo gravimetric analysis (TGA) and Differential Scanning Calorimetry (DSC) measurements were made on the instrument "Pyris-1, Perkin Elmer Thermal Analysis" at the heating rate of 10°C/min in nitrogen atmosphere for all the dihydropyrimidinones.

RESULTS AND DISCUSSION

The TGA thermo grams of RVG-9 and RVG-10 are given in Figure 3.5.1. Various thermal properties such as initial decomposition temperature (IDT), the decomposition temperature range and the maximum degradation along with the percentage weight loss and endothermic transitions are reported in Table 3.5.1.

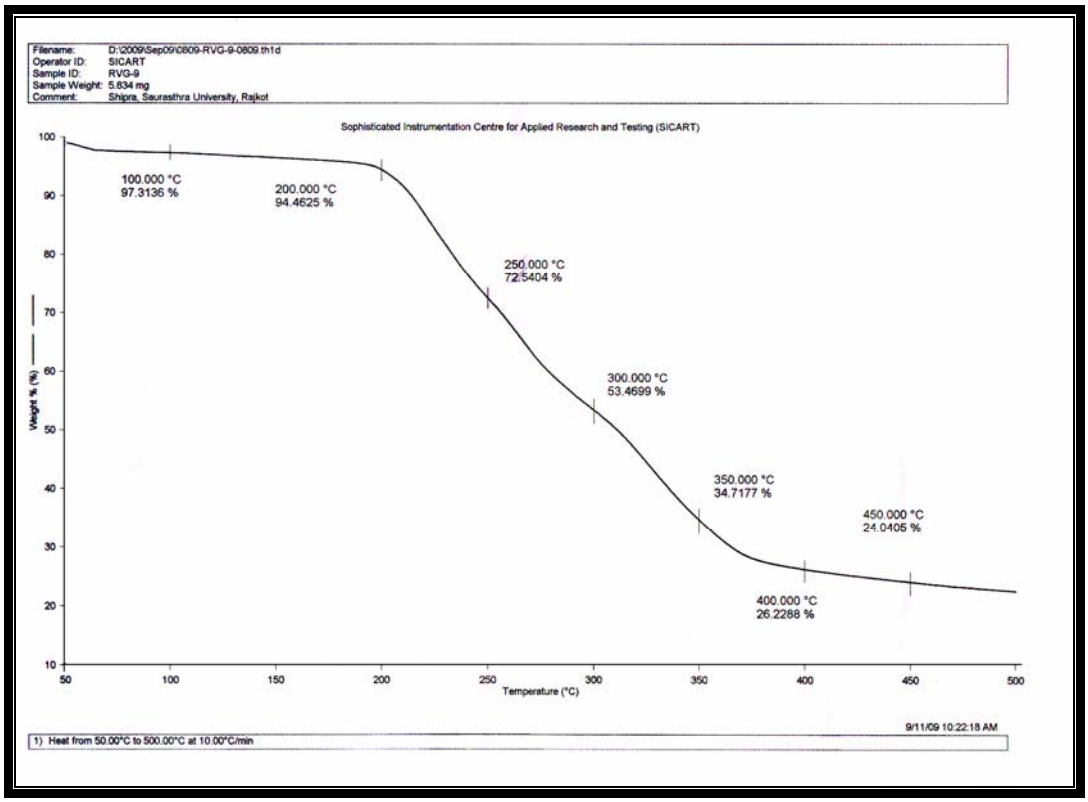
For some compounds, degradation is single step process whereas for others, it is multi step process. For RVG-1, and RVG-3, multi step degradation takes place whereas in other compounds, degradation is single step process.

Table 3.5.1 shows that RVG-9 and RVG-10 is unstable whereas RVG-6 and RVG-8 is most stable followed by RVG-4. RVG-10 has meta chloro, para flouro side chain whereas RVG-9 has two chloro groups at meta and para positions. In other compounds, various substituent groups are attached. Thus, thermal stability is affected by the substituent group. Further, the positions of substituent also affect stability of the studied compounds. When chloro group is present at meta position (as in RVG-8) stability is higher that RVG-4, containing chloro group at para position. However, the presence of chloro groups at both meta and para positions make the compound most unstable as in RVG-9. Similarly, the presence of fluoro group at para position (iRVG-6) increases the stability.

Various kinetic parameters, such as order of the degradation (*n*), energy of activation (*E*), frequency factor (*A*) and entropy change (ΔS^{o}) have also been calculated from the thermograms for each step and are reported in Table 3.5.2.

It is evident from Tables 3.5.2 that order of reaction is quite different in different steps for different dihydropyrimidinones. For single step degradation compound, order of reaction varies from 1.75 to 10.80, whereas for multi steps it varies from 2.68 to 9.31.

Figure 3.5.1: The TGA graphs of RVG-9 and RVG-10.



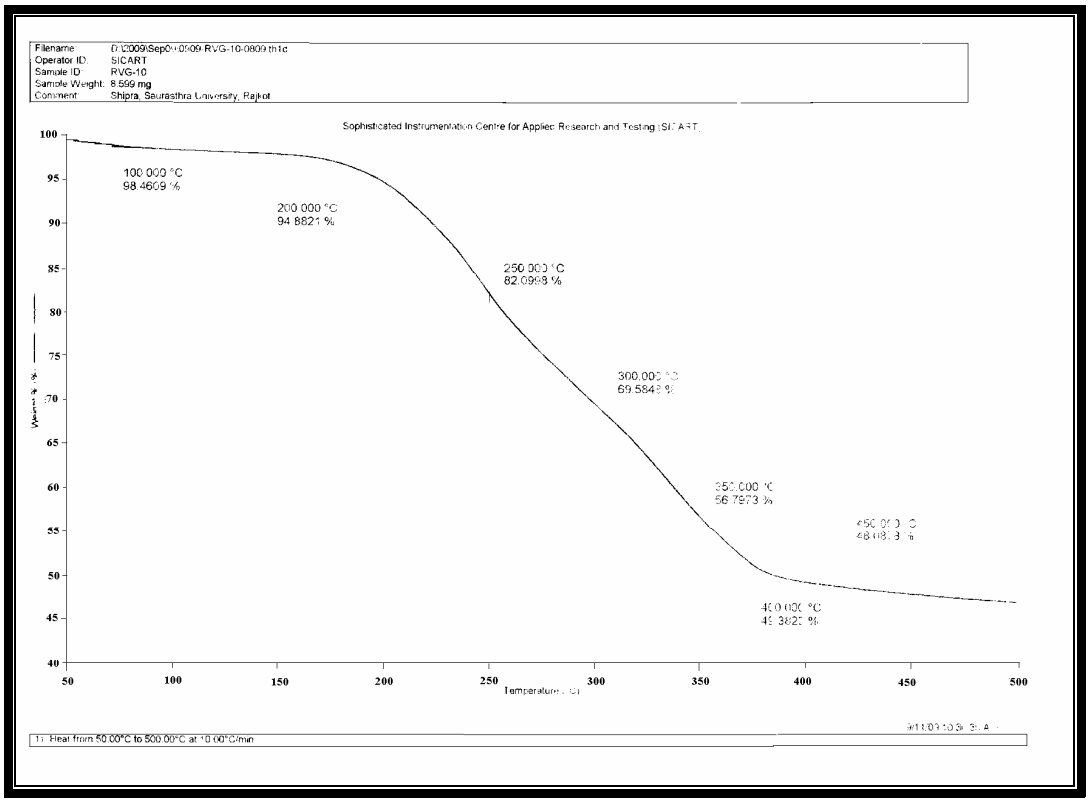


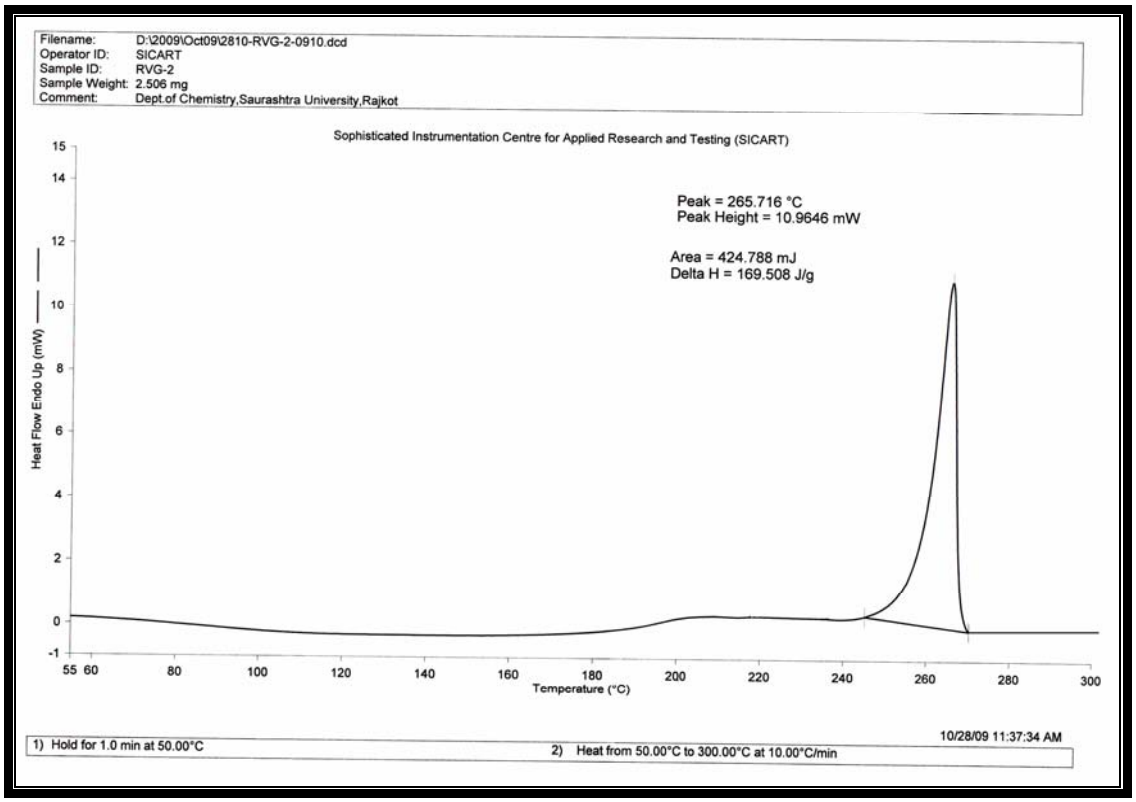
Table 3.5.1: TGA/DSC data for synthesized Dihydropyrimidinone derivatives.

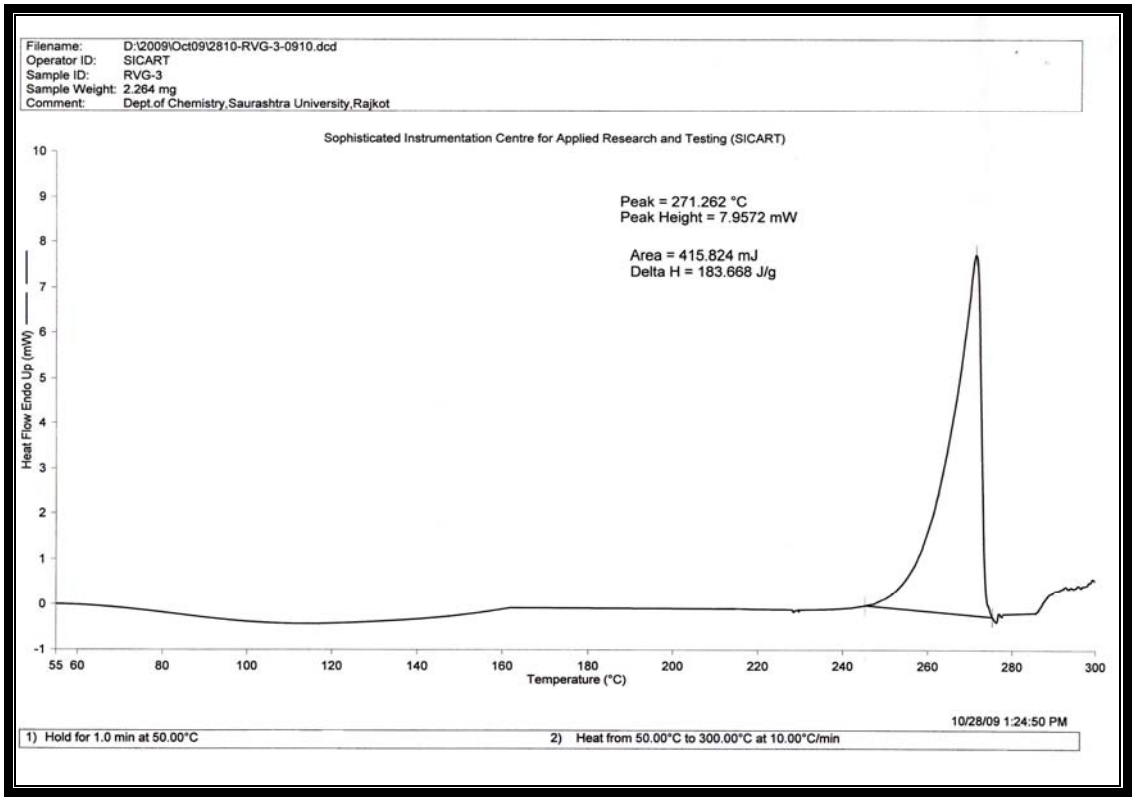
Comp. Code	*Amt. mg.*	*Initial Decomp. Temp. ^oC*	*Decomp. range ^oC*	*% Wt. loss*	*Residual Wt. Loss mg.*	*Transition*	*DSC ^0C*	*Open capillary method ^0C*	*ΔH $J.g^{-1}$*
RVG-1	0.933	150	150-700	97.96	0.913	Endo.	260.8	257	139.04
RVG-2	2.714	170	170-550	90.69	2.461	Endo.	265.7	268	169.50
RVG-3	3.247	165	165-480	59.86	1.943	Endo.	271	275	183.66
RVG-4	2.527	175	175-450	58.81	1.481	Endo.	256	253	121.27
RVG-5	2.616	145	145-510	58.85	1.539	Endo.	241	239	127.32
RVG-6	9.477	210	210-610	57.33	5.433	-	-	-	-
RVG-7	7.571	150	150-380	84.05	6.363	-	-	-	-
RVG-8	4.175	210	210-485	72.50	3.026	-	-	-	-
RVG-9	5.834	100	100-500	75.37	4.397	-	-	-	-
RVG-10	8.599	100	100-490	52.01	4.472	-	-	-	-

Table 3.5.2: The kinetic parameters of Dihydropyrimidinone derivatives.

Comp. code	*n*	*E* *kJ.mol^{-1}*	*A* *s^{-1}*	*ΔS* *J.mol^{-1}.K^{-1}*
RVG-1 1st step	1.66	339.64	3.46 X 10^{17}	234.18
RVG-1 2nd step	2.68	20.216	0.1473	-117.51
RVG-2	1.78	130.41	4.55 X 10^{7}	46.72
RVG-3 1st step	7.42	296.06	1.11 X 10^{21}	303.86
RVG-3 2nd step	9.31	26.894	2.6752	-90.88
RVG-4	8.55	171.10	5.48 X 10^{11}	125.67
RVG-5	10.80	209.76	6.34 X 10^{14}	184.39
RVG-6	9.34	2.11	0.0043	-143.46
RVG-7	3.64	50.56	734.03	-43.42
RVG-8	4.09	150.09	1.24 X 10^{11}	113.97
RVG-9	1.75	265.37	2.73 X 10^{21}	312.33
RVG-10	4.06	305.05	2.32 X 10^{24}	368.29

Figure 3.5.2: The DSC graphs of RVG-2 and RVG-3.





For single step degradation compounds, energy of activation (*E*) is maximum for RVG-10 and minimum for RVG-6. The frequency factor (*A*) also varies in the same order. For multi step degradation compounds, in first step, RVG-1 is found to be maximum whereas in second step, RVG-3 is maximum. The frequency factor A is maximum for RVG-3 in first step and minimum for RVG-1 in second step.

Further, change in entropy (ΔS^0) for all these reactions were calculated by equation (3.5.14) and are reported in Table 3.3.2. These values are both positive and negative for different compounds. The positive values of ΔS^0 indicate that the transition state is less ordered than the original compound whereas negative value of ΔS^0 corresponds to an increase in the order of transition state than the reactants. The highest negative value of ΔS^0 is in RVG-6 which has lowest energy of activation (*E*) and frequency factor (*A*). The same but opposite order has shown in RVG-10 for single step degradation.

Further, Table 3.5.1 shows DSC data along with the melting temperature determined by open capillary method. It is observed that the melting temperatures determined by the two methods are in good agreement. However, no correlation could be established between heat of reaction, kinetic parameters, melting temperature, thermal stability and substitution group.

Thus, it is concluded that thermal stability depends not only on type of substitution but also its position in aromatic ring skeleton. Further, different compounds have different rates of decomposition.

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Section-VI

Dissociation Constants

INTRODUCTION

Dissociation constants are important parameters to indicate the extent of ionization of molecules in solution. The dissociation constant or acidity constants of organic compounds play a fundamental role in many analytical procedures such as acid-base titration, solvent extraction, complex formation and ion transport[1]. It has been shown that the acid-base properties affect the toxicity [2], chromatographic retention behavior and pharmaceutical properties[3] of organic acids and bases. Much of the theoretical foundation of modern organic chemistry is based on the observation of the effects on acid-base equilibria of changing molecular structure[4].

Various workers have been reported the various method to determine the dissociation constants. Several methods for the determination of dissociation constants, such as potentiometric titration, spectrophotometric determination, conductometry and polarographic method have been reported[5-9]. Datta et al have reported the determination of dissociation constants from molar conductance[10]. Lahiri and co-workers have been reported the radiotracer method for dittermine the dissociation constants[11]. Sager and Siewers have been measured the dissociation constant of 4-aminobenzophenone from ultraviolet spectra[12]. Potentiometry is mostly used for the determination of dissociation constants of acids because it is economical of time. Further it can be used for acids of pKa range from 2 to 11 units.

For this measurement, glass and calomel electrodes have been used and carbonate free potassium hydroxide is the best alkali to use as a titrant. In contranst to potentiometry, the conductimetry provides a simple and accurate method for the determination of dissociation constants of acids without any primary and secondary buffer solutions required for calibration of the platinum electrode[13, 14].

The determination of the dissociation constant of an acid in mixtures of organic compounds with water provides useful data for the theoretical understanding of the ionization process in this media. The dissociation constants are also important for tautomeric equilibria and solvent-solute interaction[15]. The effect of solvent composition on the dissociation equilibria of

organic reagents is of great importance in chemical and biomedical analysis[16]. Dissociation constants can be a key parameter for understanding and quantifying chemical phenomena such as reaction rates, biological activity, biological uptake, biological transport, acid-base titration, solvent extraction, complex formation ion transport and environmental fate[17-19].

For water insoluble compounds, the formation constant and other thermodynamic properties are measured in purely non-aqueous organic solvent or in a mixture of two solvents, one of which may be water. A solvent mixture containing water and water miscible organic solvent is known as mixed aqueous medium. A number of works has been done in non aqueous and mixed aqueous media[20, 21].

Some of the thermodynamic parameters have also been evaluated with the help of dissociation constant [22-25]. Fazary and Taha[26] have been reported the thermodynamics of second-stage dissociation of propenoic acid derivative in different solvent mixture. Seleem et al have been reported the dissociation constant and thermodynamic parameters of Schiff bases[27]. Verma was reported the thermodynamic assessment of water from dissociation constant[28]. Das and co-workers[29] have been reported the thermodynamics of the dissociation constants of trans-cinnamic acid. Topallar and Bayrak[30] have been reported the thermodynamics of dissociation constants of cromium soap.

A literature survey shows that various workers studied the dissociation constant of a number of substances. Many researchers have been reported the dissociation constant of organic compounds, amino acids, vitamins, polymeric materials, drug molecules, metal complexes[31-43].

The importance of pyrimidine derivatives arises from their biological, medicinal and agricultural applications[44]. Uracil and Thiamine have biological importance in metabolism because some of their derivatives are building blocks for RNA and DNA[45]. 5-Fluorouracil is a drug which is available for colon, rectum and breast tumors[46]. These advantages of pyrimidines derivatives cause an interest to study the dissociation constants and thermodynamic parameters of these derivatives. Seleem et al have been reported the dissociation constants of Schiff bases of pyrimidine moiety[27].

In the present work, the dissociation constant of all synthesized dihydropyrimidinones derivatives (RVG series) are studied in DMF at different temperatures (298.15- 318.15 K) by Calvin Bjerrum pH titration technique.

EXPERIMENTAL

All solutions used for the titration are prepared using distilled water. Following are the concentrations of the solutions used for the titration. The chemicals used were of B.D.H Analar grade.

Solutions	**Concentration (M)**
Nitric acid	1.0
Sodium hydroxide	0.5
Sodium nitrate	1.0
Ligand (in DMF)	0.1

Nitric acid and sodium hydroxide were standardized by titrating with 0.1 N NaOH and 0.05 M succinic acid solution respectively.

The buffer solutions used for the calibration of pH meter were 0.05 M potassium hydrogen phthalate and 0.01 M Borax buffer.

A Systronics *pH* meter (Model No. EQ 664) was used for the pH determination. The Systronic glass electrode and a saturated calomel electrode were used as indicator and reference electrodes respectively. Before operation, the glass electrode was immersed in 0.1 M HCl for twenty minutes. Then, it was washed thoroughly with distilled water. The *pH* meter was calibrated with buffer solution of known pH. A constant temperature was maintained to ± 0.05 K by using a digital controller Nova Inst. (Model No. NV 8550 E).

Calvin Bjerrum pH titration :

The following sets of mixtures were prepared for titration:

(I) 2 ml HNO_3 (1.0M) + 4 ml water + 30 ml DMF + 4.0 ml $NaNO_3$ (1.0 M).

(ii) 2 ml HNO_3 (1.0M) + 4 ml water + 28 ml DMF + 2.0 ml ligand solution (0.1M) + 4.0 ml $NaNO_3$ (1.0 M).

Thus, total volumes (V^0) in each set = 40.0 ml and Solvent : Water ratio 60:40 (v/v). The solvent used for the study was DMF.

The above mentioned solutions were allowed to attain a definite temperature and then titrated against standard NaOH solution (0.5 M). The same experiment was repeated at different temperatures, i.e., at 289.15 K, 308.15K and 318.15K.

THEORY

In the present work, all the compounds or ligands are of *HL* type. Thus, the equilibria are,

$$L + H \leftrightarrow HL$$

In general, these equations can be represented as:

$$LH_{j-1} + H \leftrightarrow LH_j$$

The thermodynamic proton-ligand stability constant (TK_j^H) is given by:

$$TK_j{}^H = \frac{\left[LH_j\right]}{\left\{\left[LH_{j-1}\right]\left[H\right]\right\}} \quad \text{... (3.6.1)}$$

TK_j^H is reciprocal of the thermodynamic dissociation constant of the acid LH_j dissociating as:

$$LH_i = LH_{i-1} + H$$

The overall thermodynamic proton-ligand stability constant β_j^H is given by:

$$T\beta_j^H = \frac{\left[LH_j\right]}{\left[L\right]\left[H\right]^j} \quad \text{... (3.6.2)}$$

and it refers to the reaction:

$$L + JH \leftrightarrow LH_j$$

The stoichiometric proton-ligand stability constant is given by:

$$K_j{}^H = \frac{\left[LH_j\right]}{\left\{\left[LH_{j-1}\right]\left[H\right]\right\}} \quad \text{... (3.6.3)}$$

and

$$\beta_j{}^H = \frac{\left[LH_j\right]}{\left[L\right]\left[H\right]^j} \quad \text{... (3.6.4)}$$

An inert electrolyte is used to determine the stability constant in a particular salt medium. Sodium nitrate is mostly preferred as supporting electrolyte, because of very slight complexing tendency of nitrate ion. Generally, the competition between nitrate ion and the ligand under study is minor importance. The molar concentrations are used in place of activities.

For the determination of dissociation constants, Bjerrum[47] introduced a relation for the determination of $\bar{n}_H$, which is defined as average number of hydrogen bound to each ligand.

$$\bar{n}_H = \{K_1^H [H] + 2K_1^H K_2^H [H]^2 + ...JK_1^H K_2^H [H] ... K_j^H [H]^j\} / \{1 + K_1^H [H] + K_1^H K_2^H [H]^2.....K_1^H K_2^H.....K_j^H [H]^j \quad ... (3.6.5)$$

From equation (3.6.4), we can write

$$\bar{n}_H = \frac{\sum_{j=1}^{\eta} j\beta_j^H [H]^j}{\sum_{j=1}^{\eta} \beta_j^H [H]^j} \quad : \left(\beta_0^H = 1\right) \qquad \ldots (3.6.6)$$

Equation (3.4.6) is called Bjerrum formation function of the system.

The determination of dissociation constants from experimental data comprises the following three steps: (i) evaluation of formation curve of the system (ii) calculation of stoichiometric K`s of the system by direct solution of the formation function and (iii) conversion of stoichiometric constants into thermodynamic constants.

When the system consists of a ligand, which is a conjugated base of a weak acid, the pH-metric method introduced by Bjerrum has been widely used. This method is known as "Bjerrum-Calvin pH titration technique".

In this technique, the concentration of H^+ ions is measured. Thus, a large amount of data can be obtained in a short period of time. The Irving and Rossotti method[42] has some advantages, such as:

(i) Valid for both pure water and for the mixed solvents.

(ii) Conversion of pH-meter reading in to stoichiometric hydrogen ion concentration is not necessary.

(iii) Not necessary to know the stoichiometric concentration of neutral salt added to maintain the ionic strength constant.

Due to these advantages, this method is used in the present work. The pH-meter is standardized using an aqueous buffer. The *pH* (*B*) is measured for two solutions:

(1) A mixture containing a mineral acid, a chelating agent and a neutral electrolyte to keep ionic strength constant and

(2) A mixture same as above but without the chelating agent, when titrated against an alkali solution.

After each addition of standard alkali, the *pH* meter reading (*B*) is noted using a glass electrode-saturated calomel electrode combination. For both the titrations, same initial volume of the mixture and same standard alkali is used. The titration curves obtained in the above two titrations are designated as the reagent or ligand titration curve and the acid titration curve respectively.

The possible hydrolysis reactions are ignored because (i) fresh reagent solutions were used in *pH* titrations, (ii) titration times were of the order of one hour, (iii) there were no observable drifts with time in the meter readings and (iv) the concentrations of the mineral acid or alkali in the solutions were small.

Usually, a *pH*-meter calibrated with an aqueous buffer is used for aqueous solutions only. However, for the mixed aqueous media, especially aqueous dioxane solutions, van Uitert and Haas gave a relation between the glass electrode reading B in dioxane-water medium and the stoichiometric hydrogen ion concentration of the same in mixture of varied composition and ionic strength. They reported the relation:

$$-\log\left[H^{+}\right] = B + \log f + \log U_H^0 \qquad \text{... (3.6.7)}$$

where *f* is the activity coefficient of the hydrogen ions in the solvent mixture under consideration at the same temperature and ionic strength, and U_H^0 is a correction factor at zero ionic strength, which depends only on the solvent composition and temperature. U_H^0 is taken as unity in aqueous media. The meter reading in any aqueous dioxane solution can, therefore, be converted into hydrogen ion concentration using equation (3.6.7), provided that correction factor for the appropriate solvent, salt medium, and temperature, has been determined.

Equation (3.6.7) can be written as:

$$1/anti\log B = [H^{+}]\, fU_H^0 \qquad \text{... (3.6.8)}$$

$$\therefore \left[H^{+}\right] = \frac{1}{\left[anti\log B\right]\left[fU_H^0\right]} \qquad \text{... (3.6.9)}$$

Substituting for $[H^+]$ in equation (3.4.5) we get,

$\bar{n}_H$ = $(K_1^H/f\, U^0_H)[1/\text{antilog B}] + ... + ((JK_1^H\, K_2^H ... K_J^H)/(f\, U^0_H)^J)[1/\text{antilogB}]^J$

/(1+K_1^H/f U^0_H))[1/antilog B]+..+ (($K_1^H K_2^H$...K_J^H)/(f U^0_H)J)[1/antilogB] .. (3.610)

$$K_j^H = fU_H^0 . pK_j^H \quad \text{... (3.6.11)}$$

$$\beta_j^H = fU_H^0 . p\beta_j^H \quad \text{... (3.6.12)}$$

The proton-ligands constant, p_{Kj}^H can be obtained by the interpolation at half $\bar{n}_H$ values. The pH value at $\bar{n}_H$ =0.5 gives pK_1.

$$\log K_1 = \left(\bar{n}_H\right)_{0.5} \quad \text{… (3.6.13)}$$

RESULTS AND DISCUSSION

Figure 3.6.1 shows that typical titrations curve of the acid in the absence and presence of compound RVG-1 at [A] 298.15K, [B] 308.15K and [C] 318.15K. It can be seen that for the same volume of NaOH added the compound titration curves showed a lower pH value than the titration curve of free acid.

From these titration curves, the average number of protons associated with the ligand ($\overline{n_H}$) can be calculated by the following equation given by Irving and Rossotti[48].

$$\overline{n_H} = Y - \left\{\left(V''-V'\right)\left(N^0+E^0\right)\right\} \Big/ \left\{\left(V^0+V'\right)T_L^0\right\} \quad \ldots (3.6.14)$$

where Y is the number of displaceable protons per ligand molecule. For all compounds, Y is taken as one. V' and V" are the volume of alkali required at the same pH for both acid and ligand titration curves respectively. V^0 is the initial volume of the test solution.

N^0, E^0 and T^0_L are the initial concentration of the alkali, acid and ligand respectively.

The calculated values of $\overline{n_H}$ for all the studied compounds are given in Tables 3.6.1 to 3.6.3 for all temperature systems. It is evident from Tables that the values of $\overline{n_H}$ are found to be between 0 to 1 for all the compounds. suggesting thereby the presence of only one replaceable proton.

Figure 3.6.2 shows the plot of $\overline{n_H}$ values against pH for RVG-1. The pK_1^H value was evaluated at $\overline{n_H}$ =0.5 i.e., by half-integral method for all the compounds with Y=1.

Further, the $\log \bar{n}_H \Big/ \left(\bar{n}_H - 1\right)$ values are plotted against B as shown in Figure 3.6.3. The plots are straight lines from which log pK_1^H values were calculated at several B values, by the following equation:

$$\log pK_1^H = pH + \log[\overline{n_H}/(\overline{n_H} - 1)] \quad \ldots (3.6.15)$$

The calculated pk_1^H values are reported in Tables 3.6.1 to 3.6.3 for all compounds at different pH values. From these log pK_1^H values, the average

values of pK_1^H was calculated and are reported in Table 3.6.4 along with the pK_1 value evaluated by half-integral method. Further, it is evident from Table 3.6.4 that these pK_1^H values are in agreement with that obtained by half-integral method. The acidity constant decreases in the order: *p*-OCH3 > *o*-OCH3 > *p*-CH3 > 2,5-di Cl > *p*-Cl > *p*-F > *o*- OCH3 > *m*-Cl > 3,4-di Cl > 3-Cl, 4-F.

Further, the pK_1^H value decreases with increasing temperature, i.e. the acidity of the compounds increases.[49] Further, pK_1^H is minimum in RVG-10 and maximum in RVG-1 suggesting thereby maximum dissociation in RVG-10 which contains fluoride and chloride groups. RVG-1 contains $-OCH_3$ group which causes a decrease in dissociation. Thus, high stability of compound RVG-1 can be attributed to the presence of the $-OCH_3$ group in the para position relative to the amide group. The presence of para-OCH_3 group (i. e., an electron donating effect) enhances the electron density by their high positive indicative or mesomeric effect thereby increasing the stability of the compound. RVG-1 is followed by RVG-5 which also contains $-OCH_3$ group in ortho position. RVG-2 and RVG-4 are also stable which contain methyl group at para and ortho positions respectively. Similar behavior was also observed by El-Sonbati et al.[50] while studying dissociation constants of nitrogen containing hetereocyclic aldehydes. It was observed that $-OCH_3$ and $-CH_3$ groups at para position increases the stability of compounds.

The higher acidity of RVG-10 may be due to the para substitution of fluoride group which is most electronegative halogen. Further, next electronegative halogen chloride is also present at meta-position. These substitutions cause negative inductive effect which may decrease the stability of this compound. Thus, presence of different substituents influences the dissociation of the compound.

Further, some thermodynamic parameters such as enthalpy of solution, Gibb's energy change and entropy of solution have also been evaluated from dissociation constants at different temperatures for these systems.

The enthalpy changes (ΔH) for the dissociation process were evaluated[51] from the slope of the plot pK_1^H vs. 1/T.

Using the following equation, Gibbs energy changes (ΔG) have been evaluated.[51]

$$\Delta G = 2.303\ RT\ pK_1^H \quad \ldots (3.6.16)$$

From these ΔG and ΔH values, entropy values (ΔS) were calculated using the following relationship[51], assuming ΔH to be independent of temperature[52]

$$\Delta S = (\Delta H - \Delta G) / T \quad \ldots. (3.6.17)$$

All these thermodynamic parameters are reported in Table 3.6.5 for both average and half-integral methods. It is observed that for both methods, values are in good agreement with each other.

The positive value of ΔH indicates that dissociation process is endothermic and is accompanied by absorption of heat and favourable at higher temperature.[50, 52] Further, ΔG values are positive indicating thereby that the dissociation process is not spontaneous.[50, 53] However, negative value of ΔS is due to the increased order as a result of the solvation processes[50] except RVG-7.

Figure 3.6.1: The plot of pH (B) against volume of NaOH for RVG-1 in DMF at [A] 298.15K [B] 308.15K and [C] 318.15K.

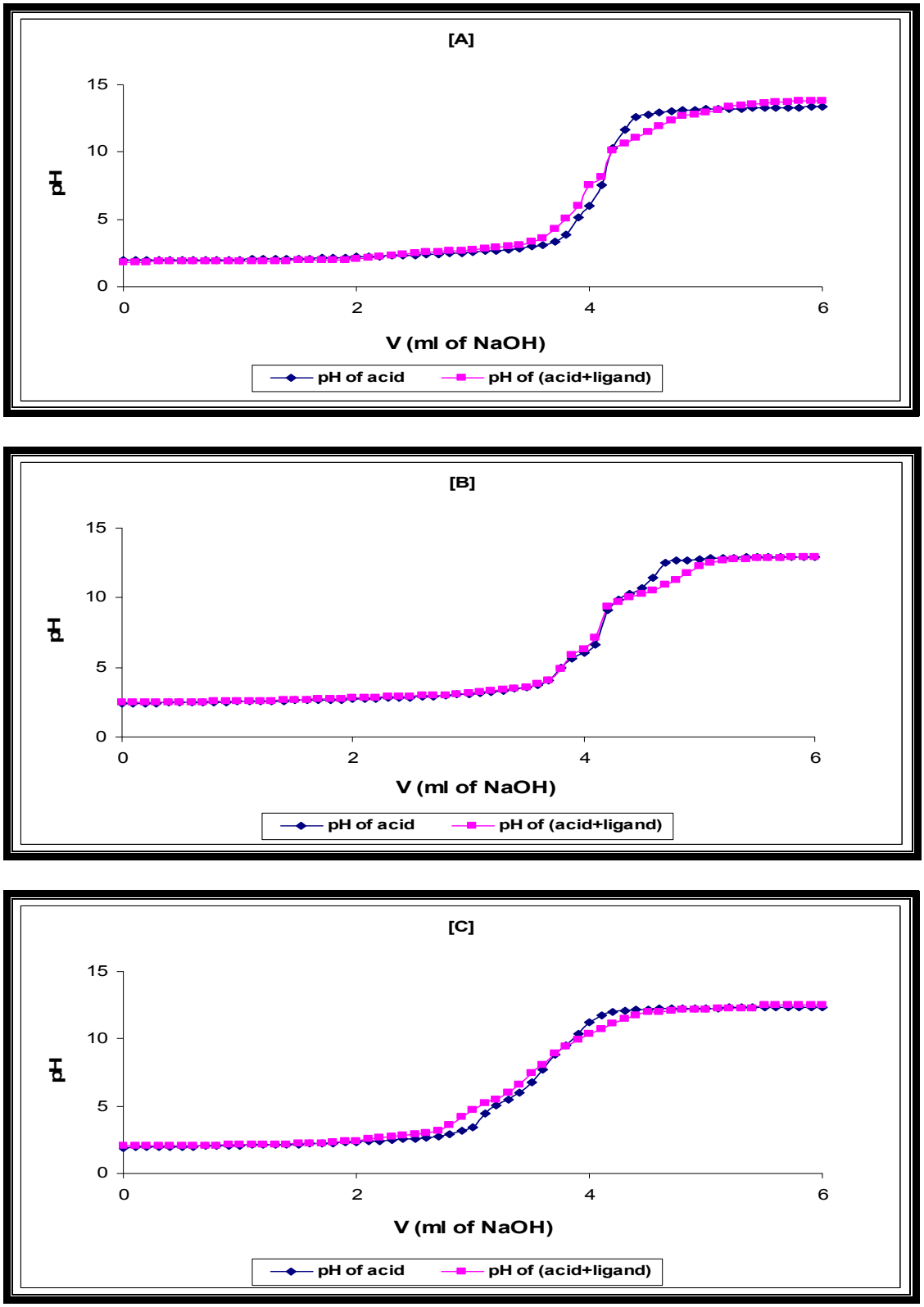


Table 3.6.1: The *pH*, n_H, pK_1^H and other terms for RVG series in DMF at 298.15K.

pH	*V'*	*V''*	*V''-V'*	n_H	log $n_H/(1-n_H)$	pK_1^H
			RVG-1			
10.2	4.1981	4.2191	0.0210	0.9478	-0.4398	11.6887
10.3	4.2035	4.2357	0.0321	0.9200	-0.4460	11.4587
10.4	4.2105	4.2581	0.0476	0.8816	-0.4527	11.3606
10.5	4.2176	4.2778	0.0601	0.8505	-0.4622	11.2721
10.6	4.2246	4.2967	0.0721	0.8209	-0.4704	11.2551
10.7	4.2316	4.3215	0.0899	0.7769	-0.4786	11.6887
10.8	4.2387	4.3389	0.1002	0.7514	-0.4914	11.4587
10.9	4.2457	4.3655	0.1198	0.7030	-0.4993	11.2741
11	4.2528	4.3886	0.1358	0.6635	-0.5153	11.2948
11.1	4.2598	4.4108	0.1510	0.6260	-0.5295	11.3237
11.2	4.2669	4.4357	0.1688	0.5821	-0.5439	11.3440
11.3	4.2739	4.4564	0.1825	0.5484	-0.5623	11.3844
11.4	4.2809	4.4827	0.2018	0.5010	-0.5777	11.4017
11.5	4.2880	4.5044	0.2164	0.4651	-0.6015	11.4393
11.6	4.2950	4.5254	0.2304	0.4308	-0.6215	11.4790
11.7	4.3032	4.5485	0.2453	0.3943	-0.6425	11.5136
11.8	4.3142	4.5743	0.2601	0.3581	-0.6673	11.5466
11.9	4.3252	4.5994	0.2742	0.3237	-0.6948	11.5800
			RVG-2			
10	4.1907	4.3011	0.1104	0.7252	-0.5078	10.4214
10.1	4.1944	4.3139	0.1195	0.7026	-0.5155	10.4733
10.2	4.1981	4.3248	0.1267	0.6847	-0.5217	10.5367
10.3	4.2035	4.3364	0.1329	0.6693	-0.5273	10.6061
10.4	4.2105	4.3594	0.1489	0.6295	-0.5425	10.6302
10.5	4.2176	4.3819	0.1643	0.5913	-0.5583	10.6604
10.6	4.2246	4.3998	0.1752	0.5642	-0.5704	10.7122
10.7	4.2316	4.4181	0.1865	0.5362	-0.5836	10.7630
10.8	4.2387	4.4292	0.1905	0.5263	-0.5885	10.8458
10.9	4.2457	4.4471	0.2014	0.4993	-0.6024	10.8988
11	4.2528	4.4697	0.2169	0.4608	-0.6240	10.9318
11.1	4.2598	4.4914	0.2316	0.4244	-0.6467	10.9677
11.2	4.2669	4.5167	0.2498	0.3793	-0.6783	10.9860
11.3	4.2739	4.5303	0.2564	0.3630	-0.6909	11.0557
11.4	4.2809	4.5455	0.2646	0.3427	-0.7076	11.1171
11.5	4.288	4.5619	0.2739	0.3197	-0.7280	11.1720
			RVG-3			
10.2	4.3361	4.4955	0.1594	0.6045	-0.5527	10.3843
10.3	4.3574	4.5226	0.1652	0.5903	-0.5588	10.4587
10.4	4.3787	4.5508	0.1721	0.5734	-0.5662	10.5285
10.5	4.3905	4.5691	0.1786	0.5574	-0.5735	10.6002
10.6	4.4093	4.5936	0.1843	0.5435	-0.5801	10.6758
10.7	4.4186	4.6091	0.1905	0.5282	-0.5875	10.7491
10.8	4.428	4.6306	0.2026	0.4984	-0.6029	10.7972
10.9	4.4373	4.6457	0.2084	0.4841	-0.6107	10.8724
11	4.4467	4.6636	0.2169	0.4632	-0.6226	10.9360
11.1	4.456	4.6805	0.2245	0.4445	-0.6339	11.0032
11.2	4.4654	4.6991	0.2337	0.4219	-0.6483	11.0631
11.3	4.4747	4.7206	0.2459	0.3918	-0.6691	11.1090
11.4	4.4841	4.7357	0.2516	0.3778	-0.6794	11.1834

pH	V'	V''	V''-V'	n_H	log $n_H/(1-n_H)$	pK_1^H
			RVG-4			
9.9	4.2879	4.4466	0.1587	0.6058	-0.5522	10.0867
10	4.2972	4.463	0.1658	0.5883	-0.5596	10.1550
10.1	4.3148	4.4872	0.1724	0.5721	-0.5668	10.2261
10.2	4.3361	4.5163	0.1802	0.5529	-0.5756	10.2923
10.3	4.3574	4.5453	0.1879	0.5340	-0.5847	10.3592
10.4	4.3787	4.5743	0.1956	0.5152	-0.5941	10.4264
10.5	4.3905	4.5926	0.2021	0.4992	-0.6025	10.4986
10.6	4.4093	4.6249	0.2156	0.4660	-0.6210	10.5408
10.7	4.4186	4.6451	0.2265	0.4391	-0.6373	10.5937
10.8	4.428	4.6629	0.2349	0.4184	-0.6506	10.6570
10.9	4.4373	4.6824	0.2451	0.3933	-0.6680	10.7117
11	4.4467	4.7035	0.2568	0.3645	-0.6897	10.7585
			RVG-5			
10.6	4.4093	4.5784	0.1649	0.5915	-0.5582	10.7609
10.7	4.4186	4.5938	0.1702	0.5785	-0.5639	10.8375
10.8	4.428	4.6085	0.1786	0.5578	-0.5733	10.9009
10.9	4.4373	4.6249	0.1876	0.5356	-0.5839	10.9620
11	4.4467	4.6409	0.1942	0.5194	-0.5920	11.0337
11.1	4.456	4.6597	0.2037	0.4960	-0.6042	11.0930
11.2	4.4654	4.6803	0.2149	0.4684	-0.6196	11.1450
11.3	4.4747	4.6976	0.2229	0.4487	-0.6313	11.2106
11.4	4.4841	4.7219	0.2378	0.4120	-0.6550	11.2455
11.5	4.4934	4.7405	0.2471	0.3891	-0.6710	11.3041
11.6	4.5044	4.7608	0.2564	0.3663	-0.6883	11.3619
			RVG-6			
10	4.1972	4.3496	0.1524	0.6207	-0.5461	10.2139
10.1	4.2149	4.3759	0.161	0.5995	-0.5549	10.2751
10.2	4.2362	4.4056	0.1694	0.5788	-0.5638	10.3380
10.3	4.2574	4.4333	0.1759	0.5628	-0.5710	10.4097
10.4	4.2787	4.4609	0.1822	0.5474	-0.5782	10.4825
10.5	4.2891	4.488	0.1989	0.5060	-0.5989	10.5104
10.6	4.3093	4.515	0.2057	0.4893	-0.6078	10.5815
10.7	4.3187	4.5312	0.2125	0.4726	-0.6172	10.6523
10.8	4.328	4.5514	0.2234	0.4456	-0.6332	10.7052
10.9	4.3374	4.5686	0.2312	0.4264	-0.6454	10.7712
11	4.3467	4.5866	0.2399	0.4049	-0.6598	10.8328
			RVG-7			
10.8	4.328	4.4784	0.1504	0.6268	-0.5436	11.0252
10.9	4.3374	4.4972	0.1598	0.6035	-0.5531	11.0825
11	4.3467	4.5114	0.1647	0.5915	-0.5583	11.1607
11.1	4.3561	4.5329	0.1768	0.5615	-0.5716	11.2075
11.2	4.3654	4.5499	0.1845	0.5425	-0.5805	11.2741
11.3	4.3748	4.5670	0.1922	0.5236	-0.5899	11.3410
11.4	4.3841	4.5858	0.2017	0.5001	-0.6020	11.4002
11.5	4.3935	4.6069	0.2134	0.4712	-0.6180	11.4500
11.6	4.4045	4.6294	0.2249	0.4429	-0.6349	11.5003
11.7	4.4194	4.6552	0.2358	0.4161	-0.6522	11.5528
11.8	4.4343	4.6810	0.2467	0.3893	-0.6709	11.6044
11.9	4.4493	4.7036	0.2543	0.3707	-0.6849	11.6701
12	4.4642	4.7329	0.2687	0.3353	-0.7140	11.7027

pH	V'	V''	V''-V'	n_H	log $n_H/(1-n_H)$	pK_1^H
			RVG-8			
10.4	4.2787	4.4408	0.1621	0.5973	-0.5558	10.5712
10.5	4.2891	4.4591	0.17	0.5778	-0.5643	10.6362
10.6	4.3093	4.4888	0.1795	0.5544	-0.5749	10.6948
10.7	4.3187	4.5065	0.1878	0.5339	-0.5847	10.7589
10.8	4.328	4.5221	0.1941	0.5183	-0.5925	10.8319
10.9	4.3374	4.5384	0.201	0.5013	-0.6014	10.9023
11	4.3467	4.5623	0.2156	0.4652	-0.6215	10.9395
11.1	4.3561	4.5801	0.2239	0.4447	-0.6337	11.0036
11.2	4.3654	4.5966	0.2312	0.4268	-0.6451	11.0718
11.3	4.3748	4.6144	0.2396	0.4061	-0.6590	11.1348
11.4	4.3841	4.6297	0.2456	0.3913	-0.6694	11.2081
			RVG-9			
9.6	3.516	3.6611	0.1451	0.6332	-0.5410	9.8371
9.7	3.536	3.6881	0.1521	0.6157	-0.5481	9.9047
9.8	3.556	3.7141	0.1581	0.6007	-0.5543	9.9774
9.9	3.576	3.7429	0.1669	0.5787	-0.5638	10.0378
10	3.596	3.7749	0.1789	0.5486	-0.5776	10.0847
10.1	3.6276	3.8170	0.1894	0.5225	-0.5904	10.1390
10.2	3.6621	3.8594	0.1973	0.5029	-0.6005	10.2051
10.3	3.6966	3.9055	0.2089	0.4741	-0.6163	10.2550
10.4	3.722	3.9376	0.2156	0.4576	-0.6260	10.3261
10.5	3.7463	3.9704	0.2241	0.4365	-0.6389	10.3891
10.6	3.7707	4.0056	0.2349	0.4097	-0.6565	10.4413
10.7	3.7951	4.0402	0.2451	0.3844	-0.6745	10.4955
10.8	3.8195	4.0762	0.2567	0.3556	-0.6968	10.5418
			RVG-10			
9.3	3.4569	3.6061	0.1492	0.6223	-0.5454	9.5169
9.4	3.4765	3.6336	0.1571	0.6025	-0.5536	9.5807
9.5	3.4961	3.6637	0.1676	0.5761	-0.5650	9.6333
9.6	3.5160	3.6902	0.1742	0.5597	-0.5725	9.7041
9.7	3.5362	3.7162	0.1802	0.5447	-0.5795	9.7779
9.8	3.5561	3.7442	0.1882	0.5247	-0.5893	9.8429
9.9	3.5760	3.7745	0.1985	0.4989	-0.6026	9.8981
10	3.5961	3.8014	0.2054	0.4817	-0.6120	9.9683
10.1	3.6276	3.8388	0.2112	0.4675	-0.6201	10.0434
10.2	3.6621	3.8816	0.2195	0.4470	-0.6324	10.1076
10.3	3.6966	3.9244	0.2278	0.4265	-0.6453	10.1715
10.4	3.7220	3.9584	0.2364	0.4052	-0.6596	10.2334
10.5	3.7463	3.9887	0.2424	0.3905	-0.6700	10.3066

Table 3.6.2: The *pH*, n_H, pK_1^H and other terms for RVG series in DMF at 308.15 K.

pH	*V'*	*V''*	*V''-V'*	n_H	$\log n_H/(1-n_H)$	pK_1^H
			RVG-1			
10.2	4.3895	4.4758	0.0863	0.7866	-0.4885	10.7665
10.3	4.4146	4.5148	0.1002	0.7524	-0.4990	10.7827
10.4	4.439	4.5511	0.1121	0.7232	-0.5085	10.8171
10.5	4.4634	4.5853	0.1219	0.6993	-0.5166	10.8664
10.6	4.4878	4.6287	0.1409	0.6527	-0.5335	10.8740
10.7	4.5063	4.6545	0.1482	0.6349	-0.5404	10.9404
10.8	4.519	4.6738	0.1548	0.6188	-0.5468	11.0105
10.9	4.5316	4.6969	0.1653	0.5932	-0.5575	11.0638
11	4.5443	4.7188	0.1745	0.5708	-0.5674	11.1238
11.1	4.557	4.7435	0.1865	0.5415	-0.5810	11.1723
11.2	4.5696	4.7715	0.2019	0.5039	-0.6000	11.2069
11.3	4.5823	4.7959	0.2136	0.4755	-0.6155	11.2574
11.4	4.5949	4.8305	0.2356	0.4219	-0.6483	11.2632
11.5	4.6057	4.8546	0.2489	0.3896	-0.6707	11.3050
11.6	4.6152	4.8716	0.2564	0.3715	-0.6843	11.3716
11.7	4.6248	4.8935	0.2687	0.3416	-0.7085	11.4151
11.8	4.6343	4.9057	0.2714	0.3352	-0.7141	11.5026
11.9	4.6438	4.9302	0.2864	0.2988	-0.7482	11.5296
			RVG-2			
10	4.3368	4.4642	0.1274	0.6839	-0.5220	10.3352
10.1	4.3632	4.4991	0.1359	0.6630	-0.5296	10.3939
10.2	4.3895	4.5386	0.1491	0.6305	-0.5421	10.4321
10.3	4.4146	4.5718	0.1572	0.6107	-0.5502	10.4955
10.4	4.439	4.6033	0.1643	0.5933	-0.5575	10.5640
10.5	4.4634	4.6387	0.1753	0.5663	-0.5694	10.6159
10.6	4.4878	4.6734	0.1856	0.5411	-0.5812	10.6715
10.7	4.5063	4.7028	0.1965	0.5143	-0.5946	10.7249
10.8	4.519	4.7199	0.2009	0.5036	-0.6001	10.8063
10.9	4.5316	4.7425	0.2109	0.4790	-0.6135	10.8636
11	4.5443	4.7656	0.2213	0.4535	-0.6284	10.9190
11.1	4.557	4.7947	0.2377	0.4132	-0.6541	10.9476
11.2	4.5696	4.8168	0.2472	0.3899	-0.6705	11.0055
11.3	4.5823	4.8335	0.2512	0.3802	-0.6776	11.0878
11.4	4.5949	4.8545	0.2596	0.3597	-0.6936	11.1495
11.5	4.6057	4.8705	0.2648	0.3470	-0.7039	11.2254
			RVG-3			
10.1	4.4317	4.5776	0.1459	0.6388	-0.5389	10.3476
10.2	4.4561	4.6078	0.1517	0.6246	-0.5445	10.4212
10.3	4.4805	4.6403	0.1598	0.6048	-0.5526	10.4848
10.4	4.5038	4.6722	0.1684	0.5838	-0.5616	10.5469
10.5	4.5226	4.6965	0.1739	0.5704	-0.5676	10.6230
10.6	4.5415	4.7271	0.1856	0.5416	-0.5810	10.6725
10.7	4.5604	4.7602	0.1998	0.5068	-0.5985	10.7118
10.8	4.5792	4.7906	0.2114	0.4784	-0.6139	10.7624
10.9	4.5981	4.8213	0.2232	0.4495	-0.6308	10.8119
11	4.6069	4.8384	0.2315	0.4291	-0.6436	10.8760
11.1	4.6145	4.8543	0.2398	0.4088	-0.6571	10.9397
11.2	4.6221	4.8679	0.2458	0.3941	-0.6674	11.0131
11.3	4.6298	4.8827	0.2529	0.3767	-0.6803	11.0812
11.4	4.6374	4.8992	0.2618	0.3548	-0.6974	11.1404

pH	***V'***	***V''***	***V''-V'***	***n_H***	***log $n_H/(1-n_H)$***	***pK_1^H***
			RVG-4			
9.8	4.366	4.5181	0.1521	0.6229	-0.5452	10.0179
9.9	4.386	4.5441	0.1581	0.6082	-0.5512	10.0910
10	4.4073	4.5685	0.1612	0.6007	-0.5543	10.1774
10.1	4.4317	4.6012	0.1695	0.5804	-0.5631	10.2408
10.2	4.4561	4.6317	0.1756	0.5655	-0.5698	10.3144
10.3	4.4805	4.6684	0.1879	0.5353	-0.5840	10.3615
10.4	4.5038	4.7086	0.2048	0.4938	-0.6054	10.3892
10.5	4.5226	4.7404	0.2178	0.4619	-0.6234	10.4337
10.6	4.5415	4.7651	0.2236	0.4478	-0.6319	10.5090
10.7	4.5604	4.7918	0.2314	0.4288	-0.6438	10.5754
10.8	4.5792	4.8178	0.2386	0.4113	-0.6554	10.6442
10.9	4.5981	4.8416	0.2435	0.3994	-0.6636	10.7228
11	4.6069	4.8558	0.2489	0.3862	-0.6732	10.7988
			RVG-5			
10.4	4.5038	4.7053	0.1529	0.6221	-0.5455	10.6164
10.5	4.5226	4.7241	0.1596	0.6057	-0.5522	10.6864
10.6	4.5415	4.743	0.1677	0.5858	-0.5607	10.7506
10.7	4.5604	4.7619	0.1754	0.5670	-0.5691	10.8171
10.8	4.5792	4.7807	0.1811	0.5531	-0.5755	10.8927
10.9	4.5981	4.7996	0.1894	0.5329	-0.5852	10.9571
11	4.6069	4.8084	0.2015	0.5031	-0.6004	11.0054
11.1	4.6145	4.8267	0.2122	0.4768	-0.6148	11.0597
11.2	4.6221	4.8452	0.2231	0.4500	-0.6305	11.1129
11.3	4.6298	4.8596	0.2298	0.4336	-0.6407	11.1840
11.4	4.6374	4.8741	0.2367	0.4167	-0.6518	11.2539
11.5	4.645	4.8899	0.2449	0.3966	-0.6656	11.3177
11.6	4.6527	4.9056	0.2529	0.3770	-0.6800	11.3818
			RVG-6			
9.8	3.8353	3.9895	0.1542	0.6131	-0.5492	9.9998
9.9	3.8471	4.0092	0.1621	0.5933	-0.5575	10.0641
10	3.8588	4.0289	0.1701	0.5734	-0.5662	10.1284
10.1	3.8706	4.0492	0.1786	0.5522	-0.5759	10.1910
10.2	3.8824	4.0688	0.1864	0.5328	-0.5853	10.2570
10.3	3.8941	4.0866	0.1925	0.5176	-0.5929	10.3306
10.4	3.9147	4.1143	0.1996	0.5000	-0.6020	10.4001
10.5	3.9441	4.1554	0.2113	0.4711	-0.6181	10.4497
10.6	3.9735	4.195	0.2215	0.4459	-0.6330	10.5057
10.7	4.0015	4.2313	0.2298	0.4255	-0.6459	10.5696
10.8	4.0162	4.2543	0.2381	0.4050	-0.6598	10.6329
10.9	4.0309	4.2774	0.2465	0.3842	-0.6747	10.6951
11	4.0456	4.3032	0.2576	0.3567	-0.6960	10.7438
			RVG-7			
9.7	3.8235	3.9814	0.1579	0.6037	-0.5531	9.8827
9.8	3.8353	4.0035	0.1682	0.5779	-0.5642	9.9365
9.9	3.8471	4.0213	0.1742	0.5630	-0.5709	10.0100
10	3.8588	4.0389	0.1801	0.5483	-0.5778	10.0842
10.1	3.8706	4.0601	0.1895	0.5249	-0.5892	10.1432
10.2	3.8824	4.079	0.1966	0.5072	-0.5983	10.2125
10.3	3.8941	4.0955	0.2014	0.4953	-0.6046	10.2918
10.4	3.9147	4.1273	0.2126	0.4675	-0.6201	10.3434
10.5	3.9441	4.1676	0.2235	0.4405	-0.6364	10.3962
10.6	3.9735	4.2076	0.2341	0.4144	-0.6533	10.4498
10.7	4.0015	4.2427	0.2412	0.3970	-0.6653	10.5185
10.8	4.0162	4.2654	0.2492	0.3772	-0.6799	10.5823

10.9	4.0309	4.2873	0.2564	0.3594	-0.6937	10.6491
RVG-8						
10.2	3.8824	4.0293	0.1469	0.6318	-0.5416	10.4344
10.3	3.8941	4.0483	0.1542	0.6136	-0.5490	10.5008
10.4	3.9147	4.0768	0.1621	0.5940	-0.5572	10.5652
10.5	3.9441	4.1139	0.1698	0.5750	-0.5655	10.6312
10.6	3.9735	4.1611	0.1876	0.5307	-0.5863	10.6534
10.7	4.0015	4.1983	0.1968	0.5080	-0.5978	10.7139
10.8	4.0162	4.2196	0.2034	0.4917	-0.6065	10.7856
10.9	4.0309	4.2444	0.2135	0.4666	-0.6206	10.8419
11	4.0456	4.2717	0.2261	0.4353	-0.6396	10.8870
11.1	4.0603	4.2998	0.2395	0.4021	-0.6618	10.9277
11.2	4.075	4.3214	0.2464	0.3850	-0.6740	10.9967
11.3	4.0897	4.3485	0.2588	0.3543	-0.6979	11.0394
11.4	4.1061	4.3695	0.2634	0.3431	-0.7072	11.1179
RVG-9						
9.4	3.7796	3.9097	0.1301	0.6731	-0.5259	9.7137
9.5	3.8101	3.9389	0.1389	0.6512	-0.5341	9.7711
9.6	3.8122	3.962	0.1498	0.6239	-0.5448	9.8198
9.7	3.8244	3.9902	0.1658	0.5838	-0.5616	9.8470
9.8	3.8366	4.0111	0.1745	0.5621	-0.5713	9.9085
9.9	3.8488	4.0344	0.1856	0.5344	-0.5845	9.9599
10	3.8610	4.0599	0.1989	0.5012	-0.6014	10.0020
10.1	3.8732	4.0921	0.2189	0.4512	-0.6298	10.0149
10.2	3.8854	4.1112	0.2258	0.4340	-0.6405	10.0847
10.3	3.8976	4.1367	0.2391	0.4009	-0.6626	10.1255
10.4	3.9242	4.1754	0.2512	0.3709	-0.6847	10.1706
10.5	3.9545	4.2169	0.2624	0.3433	-0.7070	10.2183
10.6	3.9848	4.2593	0.2745	0.3135	-0.7338	10.2596
RVG-10						
9.1	3.7184	3.8596	0.1412	0.6447	-0.5366	9.3588
9.2	3.7388	3.8895	0.1507	0.6210	-0.5459	9.4145
9.3	3.7592	3.9185	0.1593	0.5996	-0.5548	9.4753
9.4	3.7796	3.9469	0.1673	0.5796	-0.5634	9.5395
9.5	3.8104	3.9752	0.1752	0.5600	-0.5723	9.6047
9.6	3.8122	3.9983	0.1861	0.5328	-0.5853	9.6570
9.7	3.8244	4.0237	0.1993	0.4998	-0.6022	9.6996
9.8	3.8366	4.0425	0.2059	0.4833	-0.6111	9.7710
9.9	3.8488	4.0652	0.2164	0.4571	-0.6262	9.8254
10	3.8610	4.0849	0.2239	0.4385	-0.6376	9.8926
10.1	3.8732	4.1119	0.2387	0.4015	-0.6622	9.9267
10.2	3.8854	4.1311	0.2457	0.3841	-0.6747	9.9950
10.3	3.8976	4.1543	0.2567	0.3568	-0.6959	10.0440

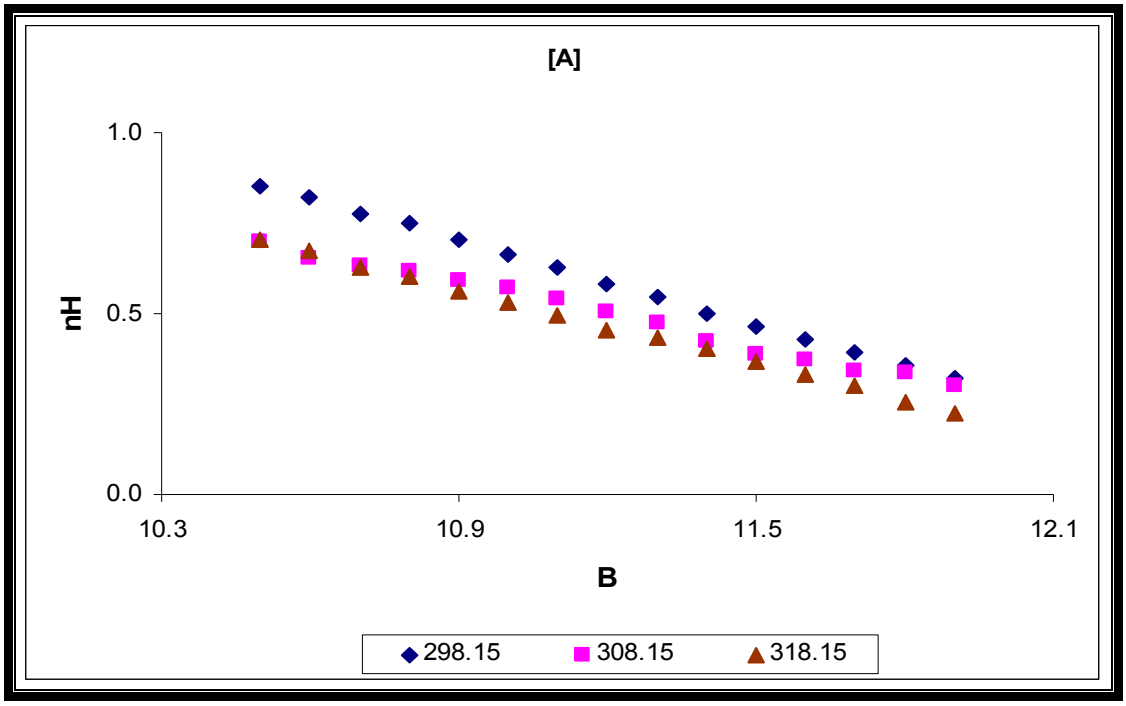
Table 3.6.3: The *pH*, n_H, pK_1^H and other terms for RVG series in DMF at 318.15 K.

pH	*V'*	*V''*	*V''-V'*	n_H	log $n_H/(1-n_H)$	pK_1^H
			RVG-1			
10.5	3.9125	4.0314	0.1189	0.7030	-0.5153	10.8741
10.6	3.9250	4.0561	0.1311	0.6727	-0.5261	10.9128
10.7	3.9375	4.0870	0.1495	0.6270	-0.5435	10.9255
10.8	3.95041	4.1102	0.1602	0.6005	-0.5544	10.9770
10.9	3.9625	4.1389	0.1764	0.5604	-0.5721	11.0054
11	3.9750	4.1644	0.1894	0.5283	-0.5875	11.0491
11.1	3.9875	4.1899	0.2024	0.4962	-0.6041	11.0934
11.2	4.0000	4.2198	0.2198	0.4532	-0.6286	11.1185
11.3	4.0172	4.2445	0.2273	0.4349	-0.6399	11.1862
11.4	4.0345	4.2743	0.2398	0.4042	-0.6603	11.2315
11.5	4.0517	4.3062	0.2545	0.3681	-0.6868	11.2654
11.6	4.0690	4.3384	0.2694	0.3316	-0.7172	11.2957
11.7	4.0862	4.3674	0.2812	0.3028	-0.7442	11.3378
			RVG-2			
10	3.8535	3.9941	0.1405	0.6476	-0.5355	10.2642
10.1	3.8651	4.0147	0.1496	0.6248	-0.5444	10.3216
10.2	3.8767	4.0361	0.1594	0.6004	-0.5545	10.3768
10.3	3.8884	4.0541	0.1657	0.5847	-0.5612	10.4486
10.4	3.9012	4.0784	0.1784	0.5530	-0.5756	10.4924
10.5	3.9125	4.0981	0.1856	0.5351	-0.5841	10.5610
10.6	3.925	4.1236	0.1986	0.5027	-0.6007	10.6046
10.7	3.9375	4.1431	0.2056	0.4853	-0.6101	10.6744
10.8	3.9510	4.1687	0.2187	0.4526	-0.6289	10.7175
10.9	3.9625	4.1861	0.2236	0.4405	-0.6364	10.7962
11	3.9750	4.2104	0.2354	0.4112	-0.6555	10.8440
11.1	3.9875	4.2351	0.2476	0.3808	-0.6772	10.8889
11.2	4.0012	4.2541	0.2541	0.3647	-0.6895	10.9591
			RVG-3			
9.8	3.8462	3.9948	0.1486	0.6272	-0.5434	10.0259
9.9	3.8718	4.0261	0.1543	0.6131	-0.5491	10.1000
10	3.8974	4.0582	0.1608	0.5971	-0.5559	10.1708
10.1	3.929	4.0976	0.1686	0.5778	-0.5642	10.2363
10.2	3.9613	4.1405	0.1792	0.5516	-0.5762	10.2900
10.3	3.9935	4.1791	0.1856	0.5359	-0.5837	10.3625
10.4	4.0286	4.2213	0.1927	0.5186	-0.5924	10.4323
10.5	4.0643	4.2654	0.2011	0.4980	-0.6031	10.4965
10.6	4.1102	4.3154	0.2154	0.4627	-0.6229	10.5351
10.7	4.4238	4.6516	0.2278	0.4359	-0.6393	10.5881
10.8	4.1476	4.3833	0.2357	0.4127	-0.6544	10.6468
10.9	4.1714	4.4129	0.2415	0.3986	-0.6642	10.7214
11	4.1952	4.4493	0.2541	0.3676	-0.6873	10.7643
			RVG-4			
9.6	3.7967	3.9434	0.1467	0.6315	-0.5417	9.8340
9.7	3.8205	3.9729	0.1524	0.6174	-0.5474	9.9079
9.8	3.8462	4.0064	0.1602	0.5981	-0.5554	9.9726
9.9	3.8718	4.0398	0.168	0.5788	-0.5638	10.0380
10	3.8974	4.0756	0.1782	0.5535	-0.5753	10.0932
10.1	3.929	4.1144	0.1854	0.5358	-0.5838	10.1622
10.2	3.9613	4.1596	0.1983	0.5038	-0.6000	10.2066
10.3	3.9935	4.2041	0.2106	0.4734	-0.6167	10.2538

pH	V'	V''	V''-V'	n_H	log $n_H/(1-n_H)$	pK_1^H
10.4	4.0286	4.252	0.2234	0.4419	-0.6355	10.2985
10.5	4.0643	4.2961	0.2318	0.4213	-0.6487	10.3622
10.6	4.1101	4.3431	0.2431	0.3936	-0.6678	10.4123
10.7	4.4238	4.6802	0.2564	0.3651	-0.6892	10.4597
10.8	4.1476	4.4085	0.2609	0.3499	-0.7015	10.5310
RVG-5						
10.2	3.9613	4.108	0.1467	0.6329	-0.5412	10.4366
10.3	3.9935	4.1481	0.1546	0.6134	-0.5490	10.5006
10.4	4.0286	4.1909	0.1623	0.5945	-0.5570	10.5662
10.5	4.0643	4.2424	0.1781	0.5554	-0.5744	10.5966
10.6	4.1012	4.2842	0.1842	0.5405	-0.5815	10.6706
10.7	4.4238	4.6194	0.1956	0.5157	-0.5939	10.7272
10.8	4.1476	4.1476	0.2018	0.4972	-0.6036	10.7951
10.9	4.1714	4.3863	0.2149	0.4648	-0.6217	10.8388
11	4.1952	4.4188	0.2236	0.4435	-0.6345	10.9014
11.1	4.2258	4.4605	0.2347	0.4162	-0.6521	10.9531
11.2	4.2581	4.5039	0.2458	0.3891	-0.6711	11.0041
11.3	4.2903	4.5492	0.2589	0.3570	-0.6957	11.0444
11.4	4.3146	4.5778	0.2632	0.3467	-0.7042	11.1248
RVG-6						
9.7	3.8186	3.9698	0.1512	0.6204	-0.5462	9.9134
9.8	3.8302	3.9897	0.1595	0.5997	-0.5547	9.9756
9.9	3.8419	4.0103	0.1684	0.5775	-0.5644	10.0357
10	3.8535	4.0283	0.1748	0.5615	-0.5716	10.1075
10.1	3.8651	4.0507	0.1856	0.5346	-0.5844	10.1602
10.2	3.8767	4.0679	0.1912	0.5207	-0.5913	10.2359
10.3	3.8884	4.0907	0.2023	0.4930	-0.6058	10.2878
10.4	3.9100	4.1135	0.2135	0.4650	-0.6216	10.3392
10.5	3.9125	4.1336	0.2211	0.4461	-0.6329	10.4061
10.6	3.9250	4.1546	0.2296	0.4250	-0.6463	10.4688
10.7	3.9375	4.172	0.2345	0.4129	-0.6543	10.5472
10.8	3.9510	4.1916	0.2416	0.3953	-0.6666	10.6154
10.9	3.9625	4.2123	0.2498	0.3750	-0.6816	10.6781
RVG-7						
9.5	3.7946	3.9514	0.1568	0.6062	-0.5520	9.6873
9.6	3.8072	3.9717	0.1647	0.5864	-0.5604	9.7517
9.7	3.8186	3.9905	0.1719	0.5685	-0.5684	9.8197
9.8	3.8302	4.0104	0.1802	0.5478	-0.5780	9.8832
9.9	3.8419	4.0293	0.1874	0.5298	-0.5867	9.9518
10	3.8535	4.0448	0.1913	0.5202	-0.5916	10.0350
10.1	3.8651	4.0616	0.1965	0.5072	-0.5982	10.1126
10.2	3.8767	4.0831	0.2064	0.4825	-0.6116	10.1697
10.3	3.8884	4.106	0.2176	0.4546	-0.6277	10.2209
10.4	3.9210	4.1234	0.2234	0.4402	-0.6365	10.2957
10.5	3.9125	4.1443	0.2318	0.4193	-0.6500	10.3587
10.6	3.9250	4.1706	0.2456	0.3850	-0.6741	10.3965
10.7	3.9375	4.1936	0.2561	0.3588	-0.6942	10.4479
RVG-8						
10	3.8535	4.0056	0.1521	0.6185	-0.5470	10.2098
10.1	3.8651	4.0234	0.1583	0.6030	-0.5533	10.2816
10.2	3.8767	4.0456	0.1689	0.5766	-0.5648	10.3341
10.3	3.8884	4.0671	0.1787	0.5521	-0.5760	10.3909
10.4	3.9010	4.0869	0.1869	0.5317	-0.5858	10.4551
10.5	3.9125	4.105	0.1925	0.5178	-0.5928	10.5309
10.6	3.9252	4.1241	0.1991	0.5014	-0.6013	10.6024
10.7	3.9375	4.1511	0.2136	0.4652	-0.6214	10.6395

pH	V'	V''	V''-V'	n_H	log $n_H/(1-n_H)$	pK_1^H
10.8	3.9530	4.1798	0.2298	0.4248	-0.6464	10.6684
10.9	3.9625	4.1979	0.2354	0.4110	-0.6556	10.7437
11	3.9751	4.2217	0.2467	0.3829	-0.6756	10.7927
11.1	3.9875	4.2396	0.2521	0.3696	-0.6857	10.8681
RVG-9						
9.2	3.7541	3.8962	0.1421	0.6428	-0.5373	9.4551
9.3	3.7676	3.9162	0.1486	0.6265	-0.5437	9.5247
9.4	3.7811	3.9359	0.1548	0.6111	-0.5500	9.5962
9.5	3.7946	3.963	0.1684	0.5770	-0.5646	9.6349
9.6	3.8074	3.9824	0.1754	0.5596	-0.5725	9.7040
9.7	3.8186	4.0120	0.1814	0.5446	-0.5795	9.7777
9.8	3.8302	4.0291	0.1989	0.5008	-0.6016	9.8014
9.9	3.8419	4.0506	0.2087	0.4764	-0.6150	9.8589
10	3.8535	4.0703	0.2168	0.4562	-0.6268	9.9237
10.1	3.8651	4.0889	0.2238	0.4388	-0.6375	9.9931
10.2	3.8767	4.1064	0.2297	0.4241	-0.6468	10.0672
10.3	3.8884	4.1252	0.2368	0.4065	-0.6587	10.1356
10.4	3.9102	4.1457	0.2457	0.3844	-0.6745	10.1954
RVG-10						
9	3.7270	3.8615	0.1345	0.6617	-0.5301	9.2913
9.1	3.7405	3.8797	0.1392	0.6499	-0.5346	9.3687
9.2	3.7541	3.9028	0.1487	0.6262	-0.5439	9.4240
9.3	3.7676	3.9224	0.1548	0.6109	-0.5500	9.4960
9.4	3.7811	3.9449	0.1638	0.5885	-0.5596	9.5553
9.5	3.7946	3.9741	0.1795	0.5491	-0.5774	9.5857
9.6	3.8071	4.0051	0.1981	0.5026	-0.6007	9.6045
9.7	3.8186	4.0231	0.2045	0.4866	-0.6093	9.6768
9.8	3.8302	4.0470	0.2168	0.4559	-0.6270	9.7232
9.9	3.8419	4.0663	0.2244	0.4370	-0.6386	9.7899
10	3.8535	4.0854	0.2319	0.4183	-0.6507	9.8568
10.1	3.8651	4.1044	0.2393	0.3999	-0.6633	9.9237
10.2	3.8767	4.1225	0.2458	0.3838	-0.6750	9.9943

Figure 3.6.2: The plot of n_H against pH (B) for [A] RVG-1 and [B] RVG-2 in DMF at different temperatures.



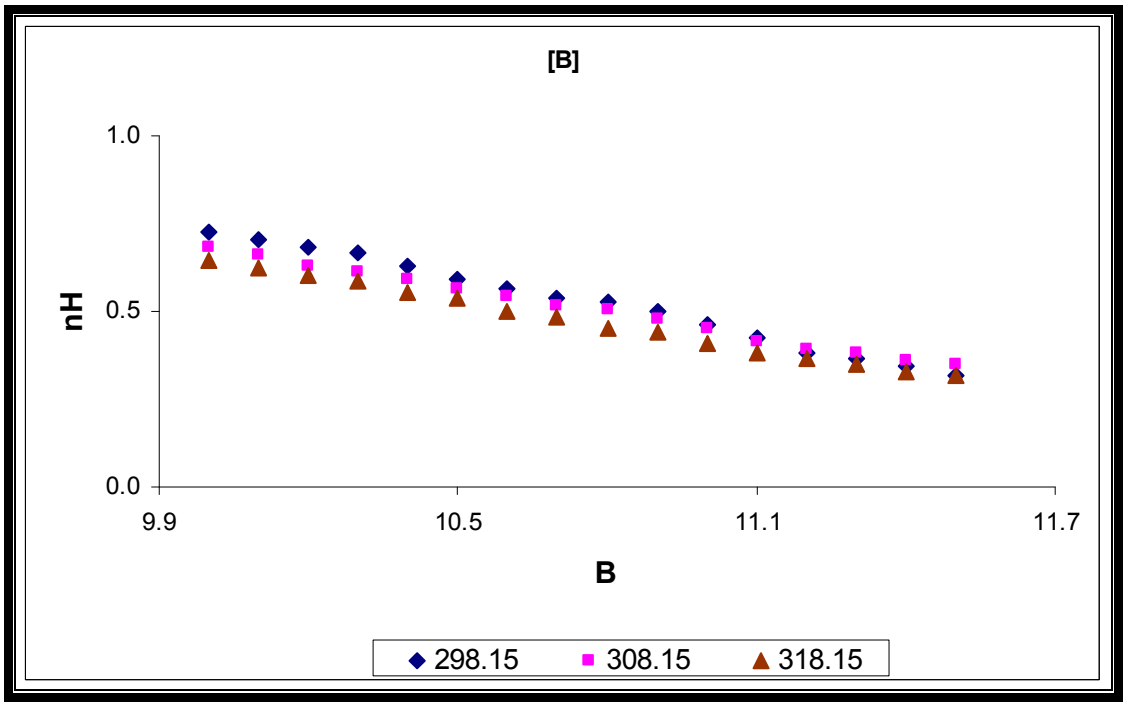
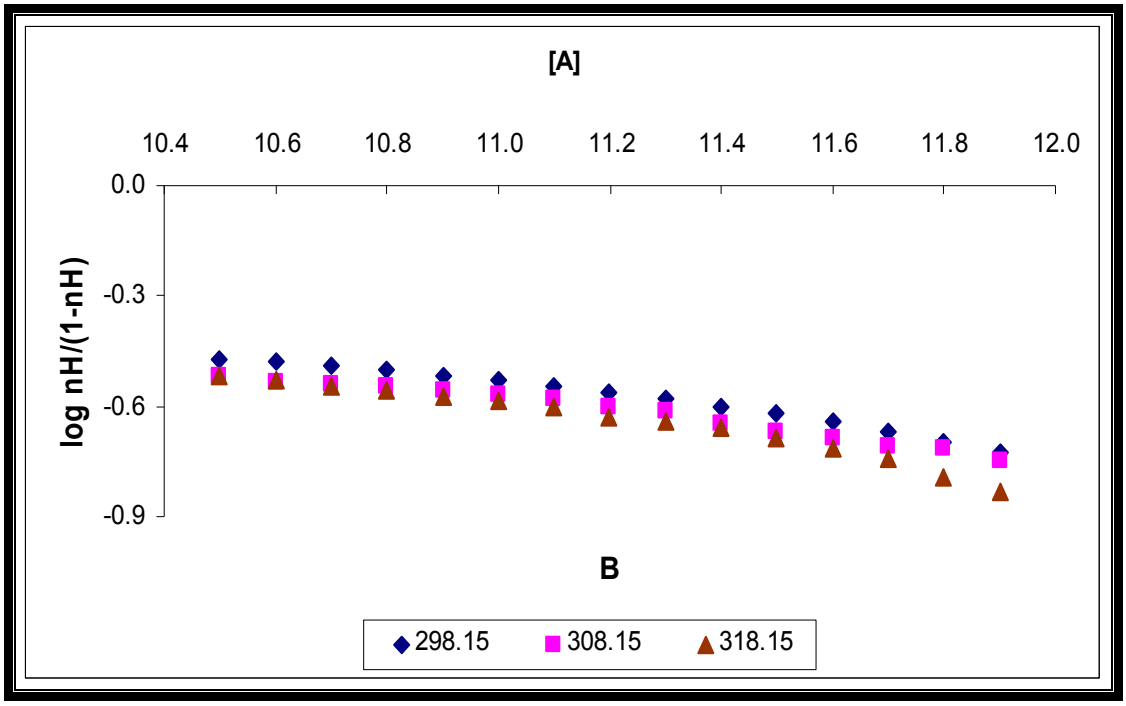


Figure 3.6.3: The plot of log $n_H/(1-n_H)$ against B for [A] RVG-1 and [B] RVG-2 in DMF at different temperatures.



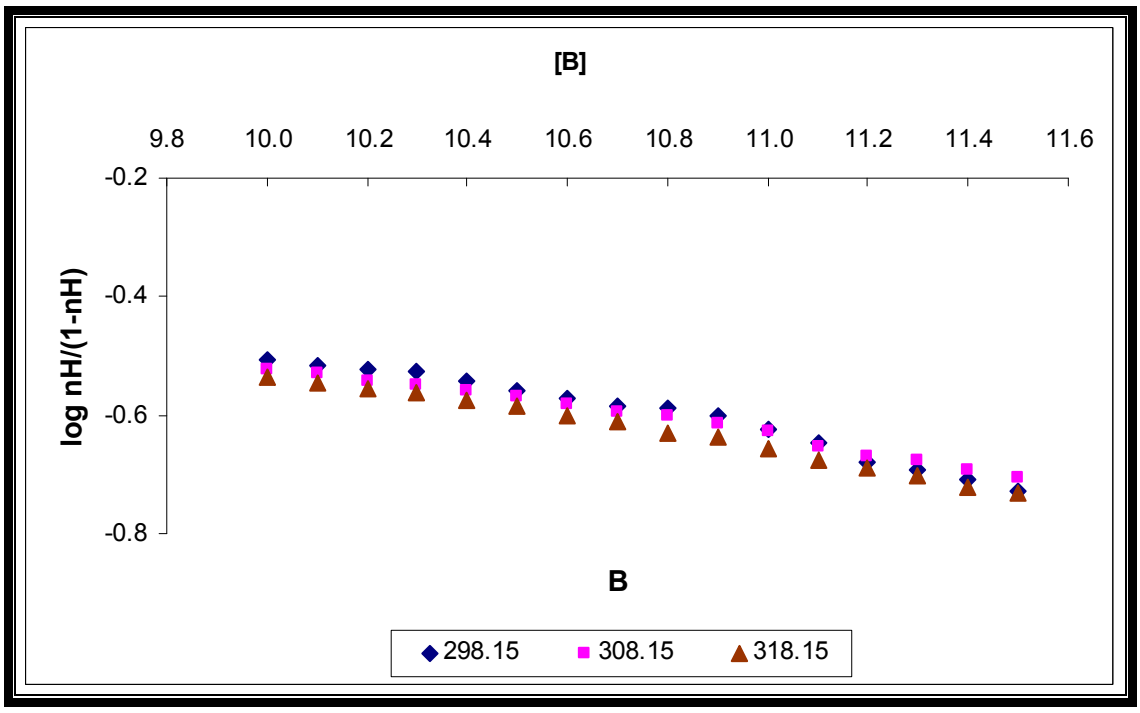


Table 3.6.4: The pK_1^H values for all the studied compounds calculated by different methods in DMF at different temperatures.

Comp. code	T/K	Half-integral method	Average method	Comp. code	T/K	Half-intergal method	Average method
		pK_1^H				pK_1^H	
RVG-1	298.15	11.44	11.41	RVG-6	298.15	10.54	10.52
	308.15	11.20	11.19		308.15	10.32	10.38
	318.15	11.08	11.09		318.15	10.26	10.29
RVG-2	298.15	10.82	10.87	RVG-7	298.15	11.32	11.35
	308.15	10.80	10.79		308.15	10.20	10.26
	318.15	10.62	10.61		318.15	9.98	10.08
RVG-3	298.15	10.76	10.79	RVG-8	298.15	10.82	10.88
	308.15	10.70	10.71		308.15	10.72	10.77
	318.15	10.40	10.41		318.15	10.48	10.57
RVG-4	298.15	10.44	10.44	RVG-9	298.15	10.16	10.20
	308.15	10.34	10.40		308.15	9.94	9.99
	318.15	10.16	10.19		318.15	9.82	9.82
RVG-5	298.15	11.0	11.07	RVG-10	298.15	9.86	9.90
	308.15	10.92	11.0		308.15	9.68	9.70
	318.15	10.74	10.78		318.15	9.66	9.63

Table 3.6.5: Thermodynamic parameters for the dissociation of RVG series in DMF-Water mixture at different temperatures for half integral and average methods.

compounds	T/K	ΔG_{Hal} kJ mol^{-1}	ΔG_{Ave} kJ mol^{-1}	ΔH_{Hal} kJ mol^{-1}	ΔH_{Ave} kJ mol^{-1}	ΔS_{Hal} J mol^{-1} K^{-1}	ΔS_{Aye} J mol^{-1} K^{-1}
RVG-1	298.15	63.34	63.17	32.79	29.16	-0.1056	-0.1176
	308.15	66.08	66.02			-0.1080	-0.1196
	318.15	67.49	67.55			-0.1091	-0.1207
RVG-2	298.15	59.90	60.18	17.99	23.50	-0.1449	-0.1268
	308.15	63.72	63.66			-0.1484	-0.1303
	318.15	64.69	64.63			-0.1468	-0.1293
RVG-3	298.15	59.57	59.73	32.44	34.28	-0.0938	-0.0880
	308.15	63.13	63.19			-0.0996	-0.0938
	318.15	63.35	63.41			-0.0972	-0.0916
RVG-4	298.15	57.80	57.80	25.33	25.33	-0.1123	-0.1220
	308.15	61.00	61.36			-0.1158	-0.1260
	318.15	61.89	62.07			-0.1149	-0.1243
RVG-5	298.15	60.90	61.28	23.50	22.52	-0.1293	-0.1214
	308.15	64.43	64.90			-0.1328	-0.1257
	318.15	65.42	65.66			-0.1318	-0.1241
RVG-6	298.15	58.35	58.24	25.42	20.92	-0.1139	-0.1291
	308.15	60.89	61.24			-0.1151	-0.1308
	318.15	62.50	62.68			-0.1165	-0.1312
RVG-7	298.15	62.67	62.83	122.52	116.18	0.2070	0.1845
	308.15	60.18	60.53			0.2023	0.1806
	318.15	60.79	61.40			0.1940	0.1722
RVG-8	298.15	59.90	60.23	30.72	28.05	-0.1009	-0.1113
	308.15	63.25	63.54			-0.1055	-0.1152
	318.15	63.84	64.38			-0.1041	-0.1142
RVG-9	298.15	56.25	56.47	30.96	34.53	-0.0875	-0.0759
	308.15	58.64	58.94			-0.0898	-0.0792
	318.15	59.82	59.82			-0.0907	-0.0795
RVG-10	298.15	54.58	54.81	18.31	24.63	-0.1255	-0.1043
	308.15	57.11	57.23			-0.1259	-0.1058
	318.15	58.84	58.66			-0.1274	-0.1069

*Hal: Half integral method

*Avg: Average method.

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Chapter-4

Biological Activities

INTRODUCTION

The extensive use of antibiotics has led to the appearance of multi-drug resistant microbial pathogens[1]. This highlights the incessant need for the development of new classes of antimicrobial agents and alteration of known drugs in such a way that would allow them to retain their resistance to the pathogen. The design of novel chemotherapeutic agents is particularly beneficial due to their dissimilar mode of action which can avoid cross resistance to known drugs.

To overcome the alarming problem of microbial resistance to antibiotics, the discovery of novel active compounds against new targets is a matter of urgency. Many of the crude drugs, which are sources of medicinal preparations, still originate from wild-growing material. However, plant-based drugs have shortened the life span of the source of material. There is a continuous search for more potent and cheaper raw materials to feed the industry.

The major classes of almost all antibiotics have encountered resistance in clinical applications[2, 3]. The increasing antibiotic resistance of Gram positive bacteria is becoming a serious problem for human beings[4]. In order to overcome this rapid development of drug resistance, new agents should preferably consist of chemical characteristics that clearly differ from those of existing agents[5].

In recent years, multiple drug resistance has developed due to indiscriminate use of existing antimicrobial drugs in the treatment of infectious diseases. In addition to this, antibiotics are sometimes associated with adverse effects on the host-like hypersensitivity. Therefore, there is a need to develop alternative antimicrobials drugs for the treatment of infectious diseases from other sources.

Similar groups/structures often exhibit similar biological activities. However, they usually exhibit different potency. The traditional structure activity relationship (SAR) is a useful tool in the search for new drugs. However, SAR is usually determined by making minor changes to the structure of the existing compound and assessing the effect on its biological activity. Similarly, structural analogy has played vital role in designing compounds with higher potency. One of such structural analogy is seen

between 4-aryl-1,4-dihydropyridines (DHPs) of the nifedipine type and dihydropyrimidines (DHPMs).

Dihydropyrimidines belong to an important group of heterocyclic compounds, which are always an attraction point for researchers because of its efficiency towards various pharmacological usages. Dihydropyrimidines have some characteristic properties like manifestations of novel structures, thermal stability, relevant biological properties, high synthesis flexibility and medicinal utility, so a wide range of dihydropyrimidines have been synthesized and extensively studied[6, 7]. Many researchers have worked on antimicrobial activity of dihydropyrimidine moiety. Fathalla and co-workers[8] reported the antibacterial and anticancer activity of pyrimidine derivatives. Mishra et al[9] have reported the antimicrobial activity of 3,4dihydropyrimidinone derivatives. Shinde and Bahekar have reported the anti-inflammatory activity of dihydropyrimidine derivatives.[10]

In the past decades, a broad range of biological effects, including antiviral , anti tumor, antibacterial and anti-inflammatory activities has been ascribed to these partly reduced pyrimidine derivatives[11]. More recently, DHPMs have emerged as orally active antihypertensive agents. A very recent highlight in this context been the identification of the structurally rather simple DHPM monastrol as a mitotic kinesin motor protein inhibitor and potential new lead for the development of anticancer drugs.

In the present chapter, antibacterial activities of the synthesized compounds have been screened against some Gram positive and Gram negative bacteria.

EXPERIMENTAL

The antibacterial activities of all synthesized compounds were studied in DMF and DMSO.

All the synthesized compounds were re crystallized prior to use. The solvents, DMF and DMSO were also purified before use by standard method[1].

For all the compounds, agar well diffusion method was used.

Test Microorganisms:

The synthesized compounds were tested for its antibacterial activity against Gram positive bacteria viz. s*taphylococcus aureus* ATCC 25923, *bacillus cereus* ATCC 11778, *bacillus megaterium* ATCC 9885 and Gram negative bacteria viz. *proteus mirabilis* NCIM 2241, *salmonella typhimurium* ATCC 23564, and *klebsiella pneumoniae* NCIM 2719.

Microorganisms were obtained from National Chemical Laboratory (NCL), Pune, India and were maintained at 4°C on nutrient agar slants.

Preparation of test compounds:

The solutions were prepared at a concentration of 1 mg/μl for all the compounds.

Preparation of the plates and microbiological assay:

The antibacterial evaluation was done by agar well diffusion method[2,3] using Mueller Hinton Agar No.2 as the nutrient medium. The agar well diffusion method was preferred to be used in this study because it was found to be better than the disc diffusion method as suggested by Parekh et al.[3] The bacterial strains were activated by inoculating a loop full of test strain in 25 ml of N-broth and the same was incubated for 24 h in an incubator at 37^{o} C. 0.2 ml of the activated strain was inoculated in Mueller Hinton Agar. Mueller Hinton Agar kept at 45^{o}C was then poured in the Petri dishes and allowed to

solidify. After solidification of the media, 0.85 cm ditch was made in the plates using a sterile cork borer and these were completely filled with the test solution. The plates were incubated for 24 h at 37^{o}C. The mean value obtained for the three wells was used to calculate the zone of growth inhibition of each sample. The controls were maintained for each bacterial strain and each solvent. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activities of these synthesized compounds.

RESULTS AND DISCUSSION

1, 4 dihydropyrimidinones

Figure 4.1 shows inhibition against Gram positive bacteria in DMSO. It is observed that against *S. aureus*, RVG-7 showed maximum inhibition and RVG-8 showed minimum inhibition. RVG-1, RVG-2, RVG-4, RVG-6, RVG-9 and RVG-10 showed no inhibition at all.

For *B. cereus*, again RVG-7 shows maximum inhibition whereas RVG-9 and RVG-10 exhibited minimum inhibition. RVG-4 and RVG-6 showed no inhibition at all.

Against *B. megaterium*, only RVG-7 shows maximum inhibition whereas RVG-10 exhibited minimum inhibition. RVG-4 showed no inhibition.

Thus, in DMSO *S. aureus* is most resistant bacteria and compound RVG-7 is the most effective compound for the studied bacteria.

Figure 4.2 shows inhibition against Gram positive bacteria in DMF. Compound RVG-7 shows maximum inhibition for all three studied Gram positive bacteria in DMF. For *S. aureus* and *B. cereus,* RVG-4 and RVG-6 shows no inhibition at all whereas in *B. megaterium*, all the compounds show inhibition.

Thus, in DMF also, *B. megaterium* is most susceptible bacteria. In both the solvents, RVG-4 and RVG-6 shows no inhibition in *S. aureus* and *B. cereus*.

The inhibition depends on the solvent, compound structure and bacterial strain. RVG-4 and RVG-6 contain o-methyl benzene and p-fluorobenzene respectively whereas RVG-7 contains 2,5-dichlorobenzene. Thus, the presence of 2,5-dichlorobenzene increases the inhibition in the studied solvents for the above mentioned bacteria.

Against Gram negative bacteria in DMSO, Figure 4.3 shows zone of inhibition for the studied compounds. Again, activity is maximum for RVG-7 all the three studied bacteria. For *K. pneumoniae*, RVG-1, RVG-4, RVG-5 and RVG-9 had no effect. For *P. mirabilis,* RVG-4 and RVG-6 showed no inhibition. Against *S. typhimurium*, only RVG-5 and RVG-7 showed inhibition and other compounds had no inhibition at all.

Figure 4.1: Antibacterial activity of 1, 4-dihydropyrimidinones against Gram positive bacteria in DMSO.

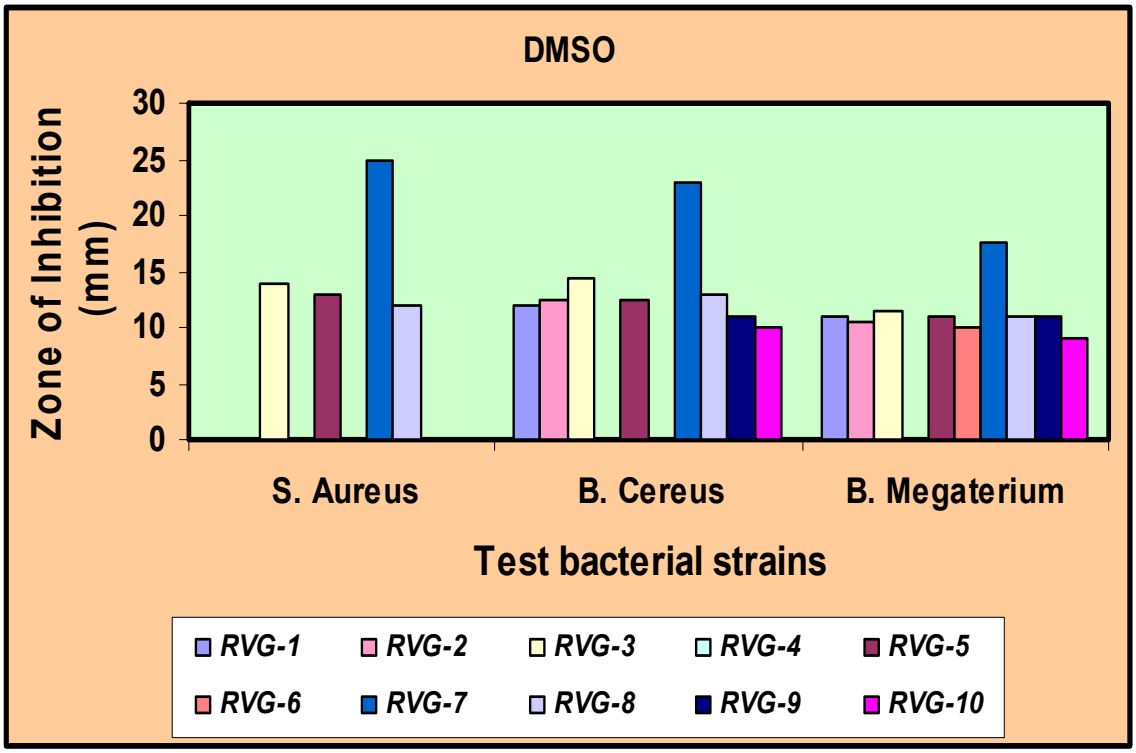


Figure 4.2: Antibacterial activity of 1, 4-dihydropyrimidinones against Gram positive bacteria in DMF.

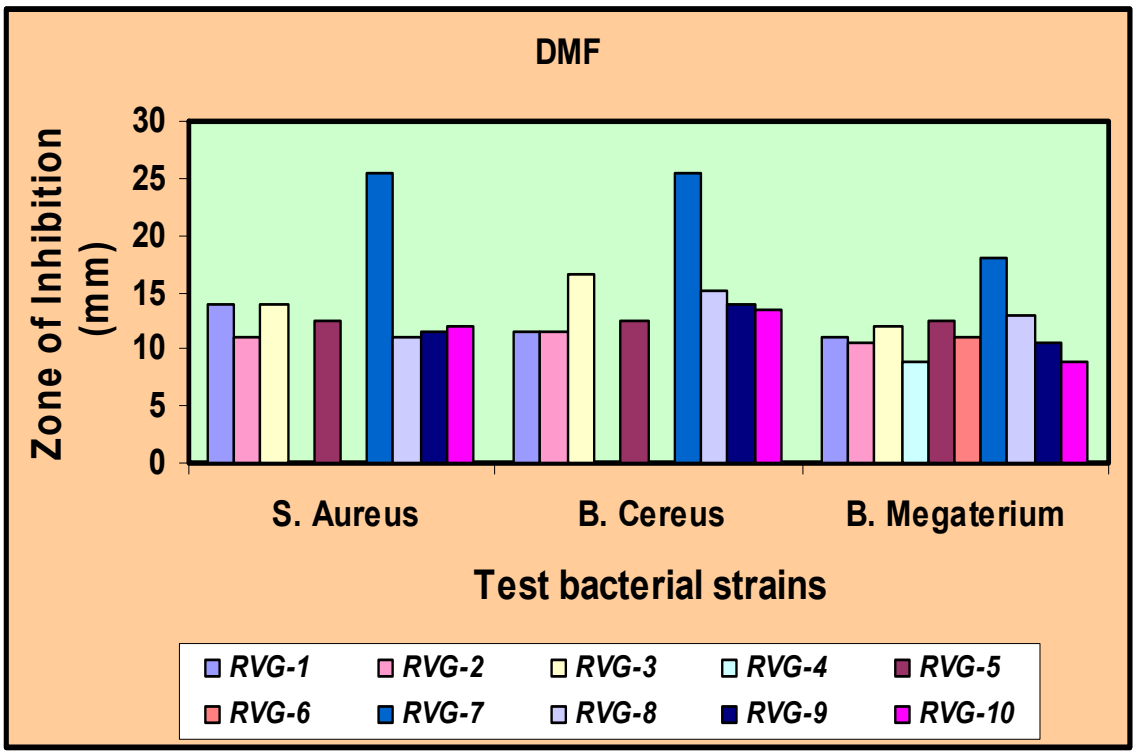


Figure 4.3: Antibacterial activity of 1, 4-dihydropyrimidinones against Gram negative bacteria in DMSO.

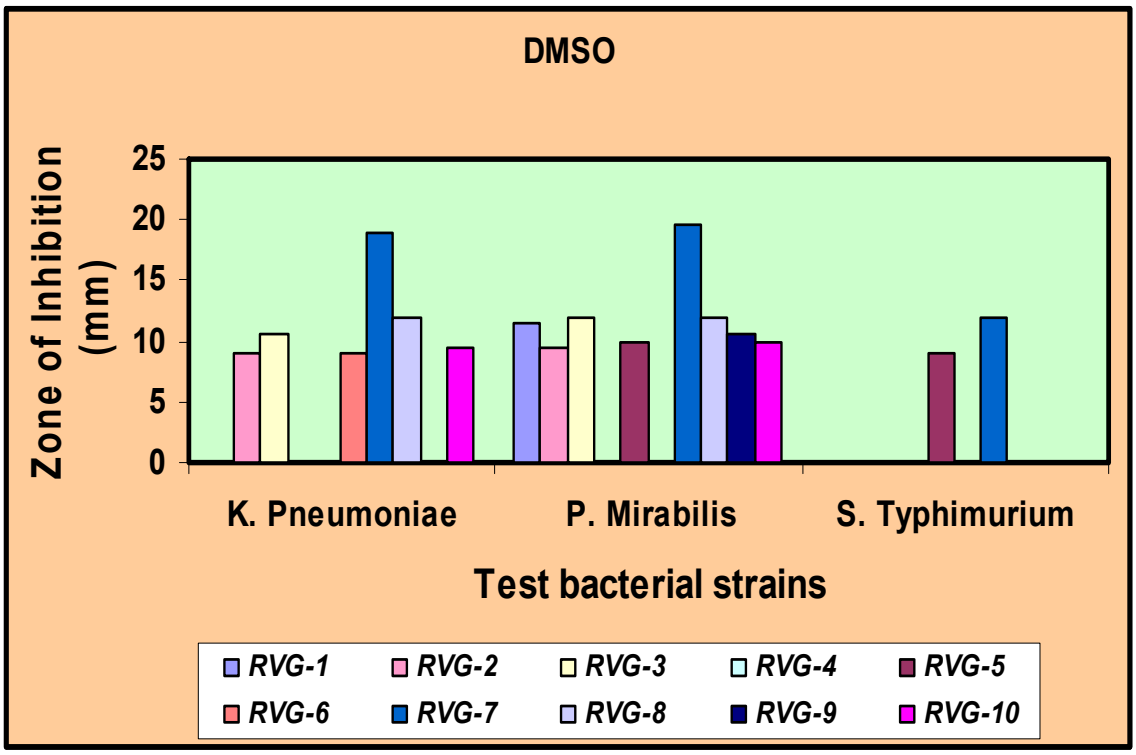
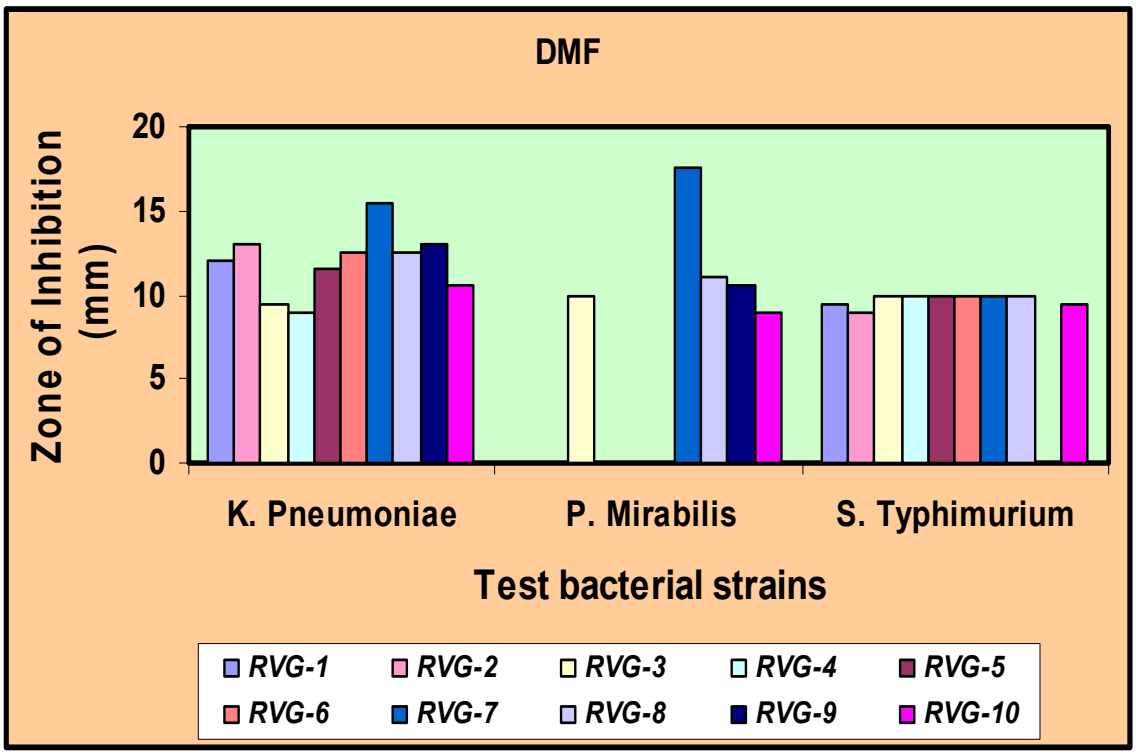


Figure 4.4: Antibacterial activity of 1, 4-dihydropyrimidinones against Gram negative bacteria in DMF.



Thus, for Gram negative bacteria also, maximum is observed by RVG-7 containing 2,5–dichlorobenzene. Whereas, RVG-4 and RVG-6 containing o-methyl and p-fluoro substitution in aromatic ring, had no effect on these bacteria. Thus, in DMSO, RVG-7 is most effective compound. *S. typhimurium* is most resistant bacteria and *P. mirabilis* is the most susceptible bacteria.

Figure 4.4 shows zone of inhibition against Gram negative bacteria in DMF. For all the three bacteria, RVG-7 showed maximum activity. For *K. pneumoniae,* all the compounds show inhibition. For *P. mirabilis,* RVG-10 shows minimum inhibition. RVG-1, RVG-2, RVG-4, RVG-5 and RVG-6 had no effect at all. Against *S. typhimurium*, inhibition is quite less in comparison to *K. pneumoniae* and *P. mirabilis.* However, minimum is observed by RVG-2 whereas RVG-9 showed no inhibition.

Thus in DMF also, *K. pneumoniae* is most susceptible bacteria and compound with -Cl substitution at 3^{nd} and 4^{th} position is most effective.

So overall, in case of RVG series although there is slight change in inhibition in the two solvents, the presence of substituents group compound plays important role in inhibition.

Dihydropyrimidinethiones

Figure 4.5 shows zone of inhibition against Gram positive bacteria in DMSO. It is observed that against S. aureus, SRG-1, SRG-2 and SRG-7 are not effective but SRG-6 shows maximum inhibition. For *B. cereus,* all compounds showed inhibition and maximum is observed by SRG-5. For, *B. megaterium,* only SRG-4 had no inhibition and SRG-5 and SRG-6 exhibited maximum inhibition.

So, overall SRG-6 containing p-flouro group in side chain is most effective in DMSO for these Gram positive bacteria and *B. cereus* is most susceptible bacteria.

In DMF, all the compounds exhibited inhibition against all the three Gram positive bacteria as evident from Figure 4.6. Again SRG-6 containing p-flouro group in side chain, showed maximum inhibition against all the three bacterial strains.

Figure 4.5: Antibacterial activity of Dihydropyrimidinethiones against Gram positive bacteria in DMSO.

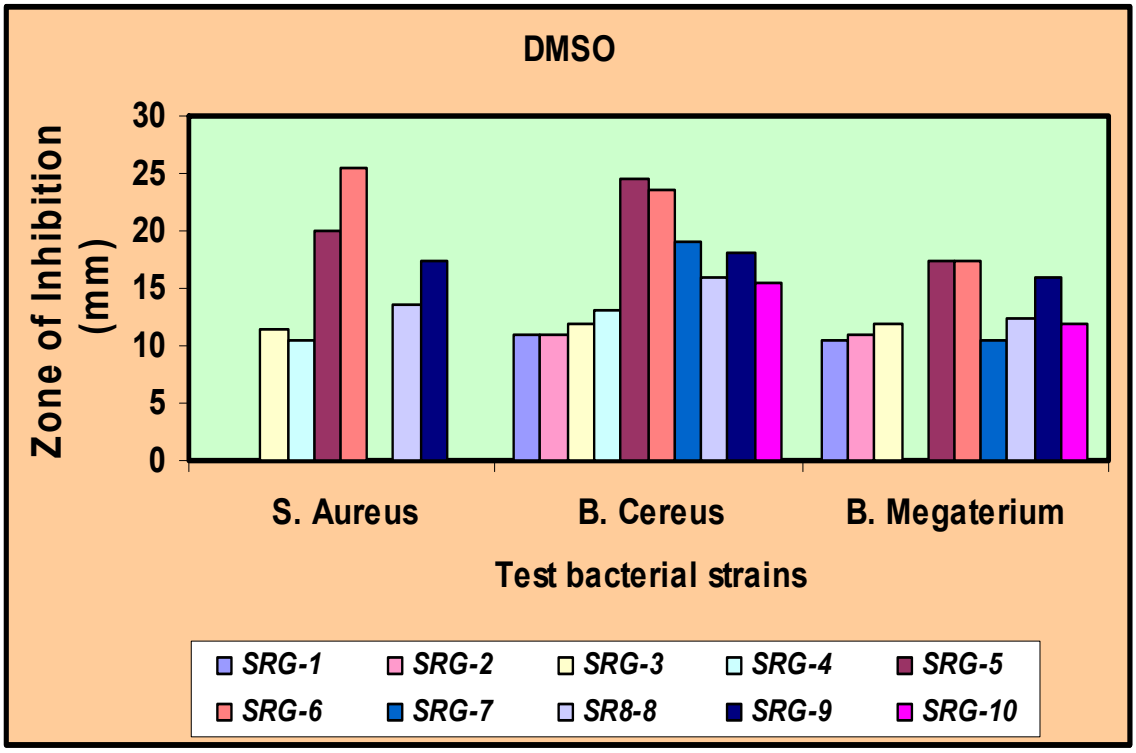


Figure 4.6: Antibacterial activity of Dihydropyrimidinethiones against Gram positive bacteria in DMF.

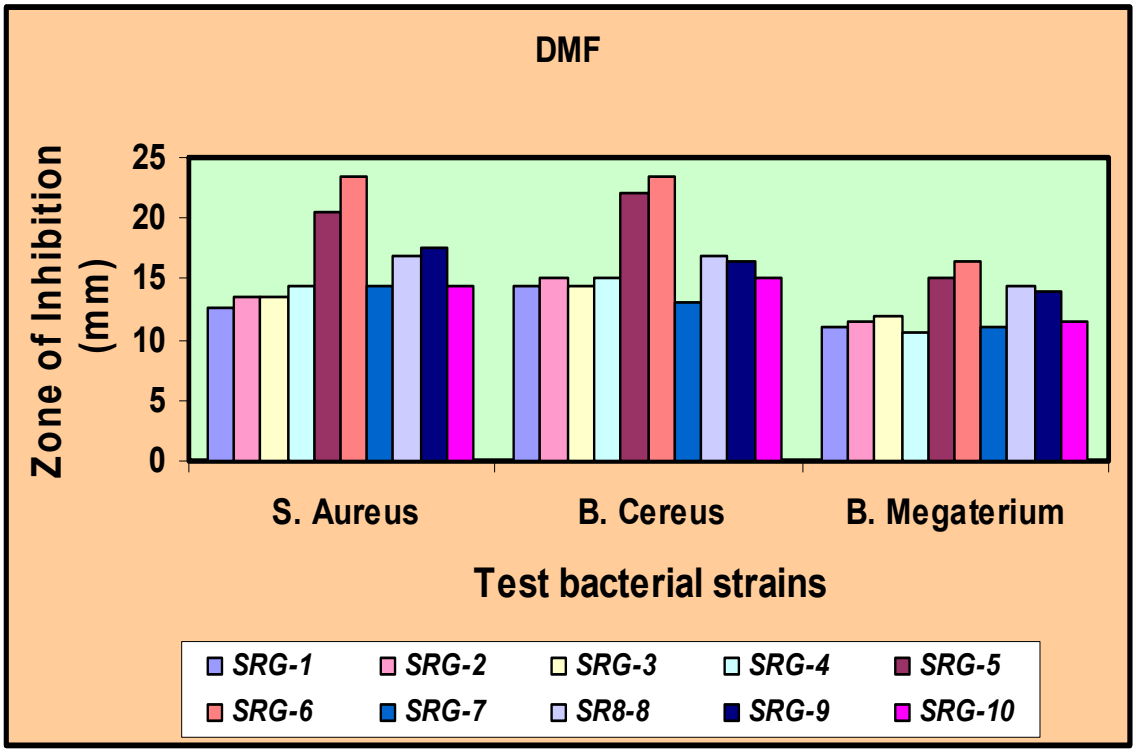


Figure 4.7: Antibacterial activity of aminopyrimidines against Gram negative bacteria in DMSO.

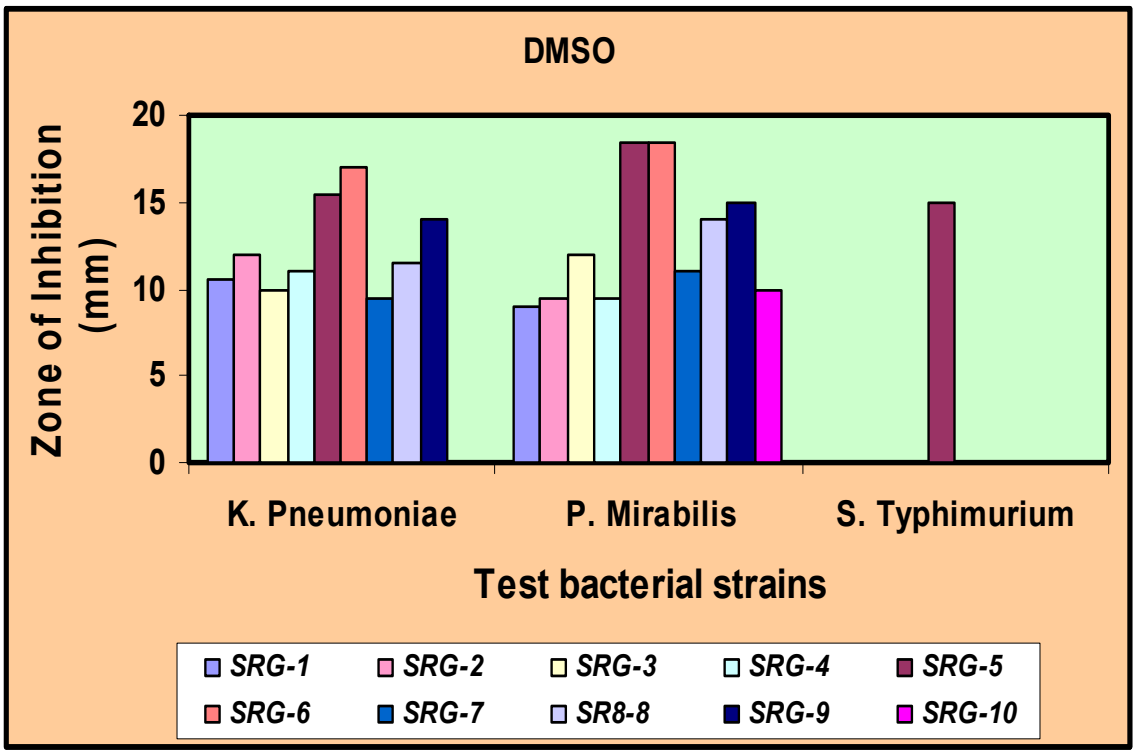
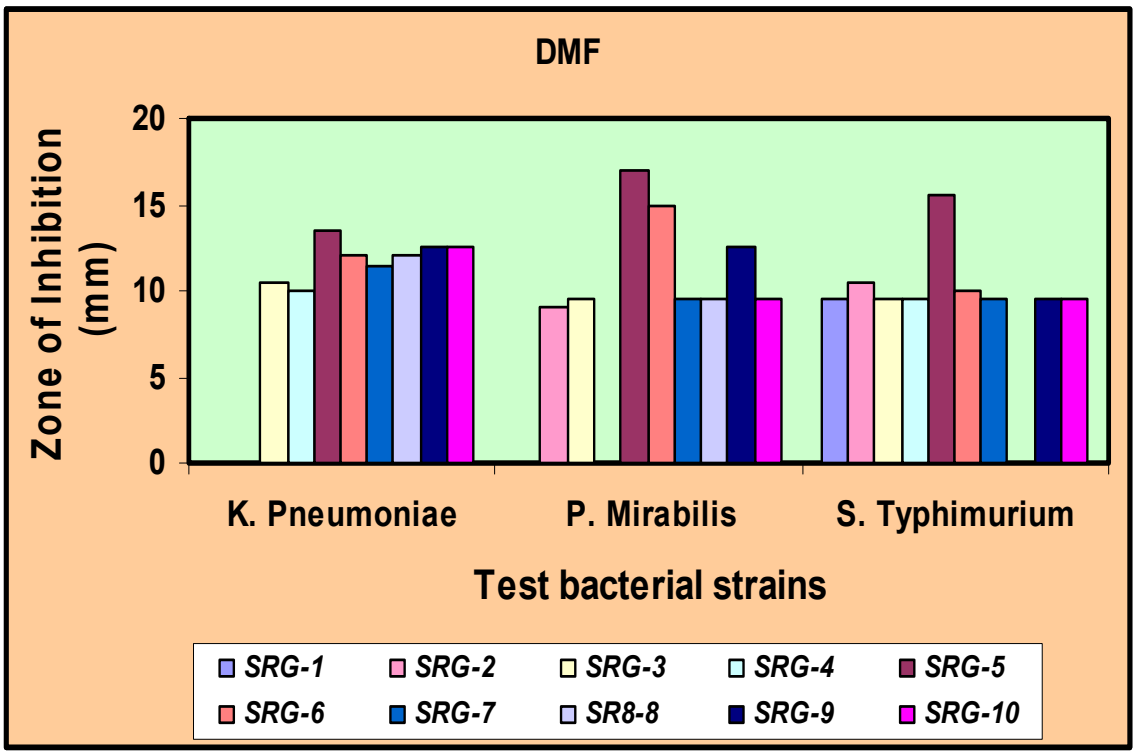


Figure 4.8: Antibacterial activity of aminopyrimidines against Gram negative bacteria in DMF.



Comparison of inhibition in DMSO and DMF shows that inhibition is greater in DMF than in DMSO.

Figure 4.7 and 4.8 show zone of inhibition against Gram negative bacteria in DMSO and DMF respectively. In DMSO, SRG-10 showed no activity against *K. pneumoniae* and SRG-5 exhibited maximum inhibition. For *P. mirabilis*, all the compounds show inhibition and SRG-5 and SRG-6 shows maximum inhibition. Against *S. typhimurium,* only SRG-5 showed inhibition. Other compounds had no effect at all. Thus, the presence of o-methoxy (as in SRG-5) and p-flouro (as in SRG-6) increases the inhibition against all the three bacterial strains.

In DMF, for all the three bacterial strains, SRG-5 shows maximum inhibition. SRG-1 and SRG-2 showed no inhibition against *K. pneumoniae*. Whereas, against *P. mirabilis,* inhibition is not shown by SRG-1 and SRG-4. For *S. typhimurium*, SRG-8 showed no activity. Overall, there is not much difference in activity of these compounds against studied bacteria. For all the studied bacteria SRG-6 shows maximum inhibition in both the solvents.

Thus, in this series of compounds, solvent and substitution play an important role in inhibition. Against both Gram positive bacteria, DMF is good solvent where almost all the substituents are effective. SRG-6 contains p-flouro substitution which is found to be most effective in both DMSO and DMF against Gram positive bacteria. Against Gram negative bacteria also, DMF is found to be good solvent.

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A Comprehensive Summary of the Work

A COMPREHENSIVE SUMMARY OF THE WORK

The present work was divided into following chapters:

CHAPTER - 1: This chapter describes the general introduction about the importance of heterocyclic compounds with aims and objective of the present work.

CHAPTER - 2: **Part-1** deals with the synthesis of dihydropyrimidinones, dihydropyrimidinethiones, N-methyl pyrimidines and tetrahydropyrimidines bearing pyrimidine moiety whereas in **Part-2** synthesis of Schiff-bases having benzothiazole moiety are described along with their physical constant data. In both the parts I and II, the characterizations of synthesized compounds are done by IR, NMR and mass spectral data. The spectra and the characteristic peak positions of IR and NMR spectra of some compounds are reported. Further, mass spectra and possible fragmentation schemes are given in both parts.

CHAPTER - 3: The physicochemical properties of synthesized dihydro pyrimidinones was also studied. The different properties are given in different sections. For the study of all physicochemical properties, DMF and DMSO are used.

Section-I: This section describes the acoustical properties of dihydropyrimidinones in solutions of various concentrations at 298.15 K. The various acoustical parameters helped to understand the different types of interactions occurring in the solutions. It is observed that for both the series, in the studied solvents, solute-solvent interactions dominate.

Section-II: In this section, the densities of dihydropyrimidinones were measured in DMF and DMSO solutions at 298.15 K. The experimental density values are found to be different than those calculated theoretically for all the studied systems, which may be due to solvation of ions in solutions. In solutions of different solvents, density is found to be different due to different

interactions. The molar refraction and refractive index of compounds are also found to be different in each solvent.

Section-III: This section deals with the conductance of studied compounds in solutions of DMF and DMSO at 298.15 K. It is observed that for all the studied compounds, conductivities are less in DMSO than in DMF. Further, all the studied compounds are found to be weak electrolytes in nature.

Section-IV: This section describes the solubility of all the studied compounds in DMF and DMSO at different temperatures (298.15 - 318.15 K). It is observed that the solubility of all the compounds increases linearly with temperature in both the solvents. Comparison of solubility of these compounds in DMF and DMSO shows that overall solubility is greater in DMF than in DMSO. The Gibb's free energy (ΔG_{sol}), enthalpy change (ΔH_{sol}) and entropy (ΔS_{sol}) of different solutions have also been evaluated. ΔH_{sol} and ΔG_{sol} values are found to be positive whereas ΔS_{sol} values are negative. Positive ΔH_{sol} indicates endothermic dissolution of compounds. Whereas positive ΔG_{sol} suggests that the dissolution process is not spontaneous. Further, the negative values of entropy indicate less random ness in solutions.

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Section-V: The thermal properties of synthesized dihydropyrimidinones are described in this section. DSC and TGA thermo grams were scanned at the heating rate of 10^0 C per minute. Out of ten studied compounds, multi-step degradation takes place in RVG-3 whereas others decompose by single step. Further, RVG-9 and RVG-10 are found to be most unstable whereas RVG-6 and RVG-8 are most stable followed by RVG-4. All the studied compounds have the same central moiety but different substituents. Thus, stability is affected by different substituent groups. RVG-10 has meta-chloro and para flouro groups whereas RVG-9 has two chloro groups at meta and para positions which decreased the stability. RVG-6 has a flouro group at para positin and RVG-8 has chloro group at meta position. Further, the position of substituent affects stability of the studied compounds.

Further, the melting points determined by DSC and by open capillary methods are found to be in good agreement. The heat of reaction is found to be maximum for RVG-3 and minimum for RVG-4. However, no correlation could be established between heat of reaction, kinetic parameters, melting temperature, thermal stability and substitution groups.

Various kinetic parameters such as order of reaction, energy of activation, frequency factor and entropy change were also calculated for each step. The order of reaction is quite different in different steps for different compounds. Further, the change in entropy values is found to be both positive and negative in different steps. The positive values of entropy change indicate that the transition state is less ordered than the original compound whereas negative value of entropy change corresponds to an increase in the order of transition state than the reactants.

Section-VI: In this section, the dissociation constants of dihydropyrimidinones in water-DMF and water-DMSO mixtures are reported at 298.15 K, 308.15 K and 318.15 K. The dissociation or acidic constant depends not only on the solvent but also on the type of substituent groups present in the compound. Different groups interact differently with the solvent, which affect their dissociation.

Further, the acidity constant value decreases with increasing temperature. Further, acidic constant is minimum in RVG-10 and maximum in RVG-1 suggesting thereby maximum dissociation in RVG-10 which contains fluoride and chloride groups. RVG-1 contains $-OCH_3$ group which causes a decrease in dissociation. Thus, presence of different substituent groups influences the dissociation of the compound.

Further, some thermodynamic parameters such as enthalpy of solution (ΔH), Gibb's energy change (ΔG) and entropy of solution (ΔS) have also been evaluated from dissociation constants at different temperatures. All these thermodynamic parameters are reported in Table 3.6.5 for both average and half-integral methods. It is observed that for both methods, values are in good agreement with each other.

The positive value of ΔH indicates that dissociation process is endothermic and is accompanied by absorption of heat and favorable at higher temperature. Further, ΔG values are positive indicating thereby that the dissociation process is not spontaneous. However, negative value of ΔS is due to the increased order as a result of the solvation processes except RVG-7.

CHAPTER - 4: The antibacterial activities of the synthesized compounds in DMF and DMSO are explained in this chapter. Different Gram positive and Gram negative bacterial strains behave differently in different solvents. Further, presence of different substituents also affects inhibition.

List of Papers

List of Papers

Published Papers

(1) "Solubility of Enrofloxacin Sodium in various solvents at various Temperature." S. Baluja, R. Bhalodia, M. Bhatt, N. Vekaria and **R. Gajera**. *J. Chem. Eng. Data*, **2008**, 53, 2897-2899.

(2) "Solubility of Difloxacine in Acetone, Methanol and Ethanol from (293.15 to 313.15 K)." S. Baluja, **R. Gajera**, R. Bhalodia, N. Vekaria, and M. Bhatt. *J. Chem. Eng. Data*, **2009**, 54, 1091-1093.

(3) "Synthesis and Ultrasonic Studies of Some Dihydro Pyrimidines in Different Solvents at 298.15 K." **R. Gajera**, R. Bhalodia and S. Baluja. *Int. J. App. Chem*., **2009**, 5(1), 47-55.

(4) "Acoustical properties of Schiff bases solutions in DMF." S. Baluja, K. P. Vaishnani, **R. Gajera** and N. Kachhadia. *Latin Amer. Appl. Res*. (LAAR), 2009.

(5) "Adiabatic Compressibilities of some synthesized derivatives of dihydro pyrimidines in N, N-Dimethylformamide and Dimethylsulfoxide at 298.15 K." **R. Gajera**, R. Bhalodia and S. Baluja, *Russ. J. Phys. Chem*., **2010**, 85(5), 1-5.

(6) "Solubility of Cholesterol in some alcohols from 293.15 to 318.15 K." S. Baluja, **R. Gajera**, N. Vekariya, M. Bhatt and R. Bhalodia. *Scholar Res. Lib., Arc. Apl. Sci. Res*., **2009**, 1(2) 263-270.

Accepted Papers

(1) "Solubility of Biologically Active Chalcones in 1,4-Dioxane and *N*,*N*-Dimethyl Formamide from (298.15 to 318.15) K." **R. Gajera**, A. Kulshreshtha and S. Baluja. *J. Chem. Eng. Data*, Accepted, **2009**.

(2) "Synthesis and Acoustical studies of some chalcones of Furaldehyde in different solvents at 308.15 K." **R. Gajera**, N. Vekaria, A. Kulshrestha and S. Baluja. *Int. J. App. Chem*., Accepted, **2009**.

(3) "Solubility of some synthetic Dihydropyrimidines in DMF at (298.15 to 318.15 K)." **R. Gajera**, R. Bhalodia and S. Baluja. *Int. J. Appl. Chem*., Accepted, **2009.**

(4) "Solubility of some synthetic dihydropyrimidines in dimethylsulfoxide at (298.15 to 318.15) K." **R. Gajera**, R. Bhalodia and S. Baluja. *Int. J. Pure App. Phys.*, Accepted, **2009**.

(5) "Synthesis and antibacterial activity of some chalcones." **R. Gajera**, S. Baluja, N. Godvani, S. Chanda, Y. Vaghasiya, J. Parekh, and M. Bhatt. *J. Ind. Chem. Soc*., Accepted, **2009**.

(6) "Synthesis, characterization and antibacterial activity of some thiazolidinones." **R. Gajera**, S. Baluja, N. Godvani, S. Chanda, Y. Vaghasiya, J. Parekh, and M. Bhatt. *J. Chem. Pharma. Sci*., Accepted, **2009**.

(7) "Solubility of Ofloxacin in 1, 2 dichloromethane, chloroform, carbon tetrachloride and water from (293.15 to 313.15) K" S. Baluja, **R. Gajera**, R. Bhalodia, M. Bhatt and N. Vekariya. *J. Chem. Eng. Data*., Accepted, **2009**.

(8) "Density and Refractive index of some Dihydropyrimidines derivatives in DMF and DMSO at 298.15 K." **R. Gajera**, R. Bhalodia and S. Baluja. *Phys. Chem.: An Ind. J*., Accepted, **2009**.

(9) "Solubility of 5-amino salicylic acid in different solvents at various temperatures." A. Patel, A. Vaghasiya, **R. Gajera** and S. Baluja. *J. Chem. Eng. Data.* **2010**

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(1) "Solubility of a pharmacological intermediate drug Isatin in different solvents at various temperatures." **R. Gajera**, R. Bhalodia, M. Bhatt, N. Vekariya and S. Baluja. *J. Chem. Eng. Data.*

(2) "Determination of some Thermodynamic parameters of dihydropyrimidine derivatives by dissociation constant." R. Bhalodia, **R. Gajera** and S. Baluja. *Russ. J. Phys. Chem*.

(3) "Synthesis and antimicrobial screening of 1, 6-dihydropyrimidine derivatives." S. Baluja, **R. Gajera,** A. Kulshrestha, A. Patel, S. Chanda, Y. Vaghasiya, Y. Barvaliya.